CASE REPORT

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Fatal Intoxication by Tocainide

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ABSTRACT: A 26-year-old woman committed suicide by ingestion of a large quantity of tocainide, a recently developed oral antiarrhythmic agent with chemical similarities to lidocaine. Blood and bodily fluid analysis by thin-layer chromatography, high pressure liquid chromatography, and mass spectroscopy confirmed the presence of tocainide, with a serum level of 68 mg/L, nearly 7 times the upper recommended therapeutic level for this drug. Tocainide was also detected at significant levels in vitreous fluid and bile. Although the mechanism of death from tocainide intoxication in animal studies is related to central nervous system toxicity, the presentation of ventricular tachyarrhythmias with coma in this patient suggests that tocainide at high levels may have primary myocardiotoxicity in humans.

KEYWORDS: pathology and biology, toxicology, suicide, tocainide

Tocainide (Tonocard, Merck, Sharpe & Dohme) is a Class IB antiarrhythmic agent that was first marketed in November 1984 and is used for suppression of symptomatic or chronic ventricular arrhythmias [*1*]. It has a structural similarity to lidocaine (Fig. 1) and similar cardiophysiologic actions. The structure of tocainide prevents the extensive first-pass hepatic metabolism that is prominent with lidocaine, and its virtual 100% oral bioavailability allows therapeutic applications that are impossible with conventional lidocaine usage. Tocainide, like lidocaine, has adverse effects which are associated especially with long-term treatment. However, a recent search of the medical literature disclosed no reported cases of fatal overdose from this relatively new drug. Herewith is delineated a suicidal ingestion of tocainide, with accompanying information regarding analysis techniques and identification parameters of this drug.

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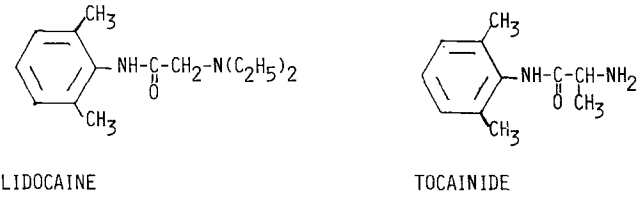

FIG. 1—*Comparative structures of lidocaine and tocainide.*

Case Report

A 26-year-old Native American (Navajo) woman was found unconscious and unresponsive, lying supine on the bathroom floor. Her family had left on an overnight trip at about 7:00 p.m. the previous day, leaving her with her two small children, and she was discovered upon their return at about 5:00 p.m. on the following day. She had been upset over a recent separation from her husband. Two notes were found at the scene, addressed to her family and her husband's supervisor, expressing suicidal intent and giving instructions on the disposition of her children. She had no prior suicide attempts nor had apparently expressed intent to take her own life at any time previously. Ethanol containers were found in the house, as well as a partially empty container of Alka Seltzer tablets. No other drugs or medication containers were within the home.

She was transported to the nearest United States Public Health Service hospital, arriving at 8:03 p.m. She had no detectable vital signs and was promptly intubated and given assisted ventilation. The cardiac monitor revealed ventricular fibrillation, which soon degenerated into asystole and electromechanical disassociation. She was aggressively resuscitated with epinephrine, bicarbonate, atropine, and Narcan®, and transiently regained a weak pulse and left bundle branch block rhythm, but shortly thereafter became asystolic again. She was pronounced dead at 9:01 p.m.

Autopsy Examination

A complete autopsy was performed 36 h after death, with significant anatomic findings solely of mild pulmonary edema and vascular congestion, acute and mild chronic hemorrhagic gastritis, and upper anterior bilateral rib fractures (typical of resuscitative external cardiac compression). No evidence of previous suicidal attempts (hesitation marks) was identified.

Toxicologic Analysis

A preliminary screen of the antemortem blood samples taken during the Emergency Room admission disclosed an ethanol level of 0.034 G%, and a salicylate level of 36 mg/L.

Thin-Layer Chromatography (TLC)

Two millilitres of sample were extracted at pH 8.8 into ten millilitres of a solution of chloroform/isopropyl alcohol (96/4). This extract was taken to dryness and reconstituted in 50 μL of methanol. Five microlitres of sample were spotted on two different ten-by ten-centimetre thin-layer plates (Merck #5635 silica gel 60 F-254). These plates were developed to the 5-cm mark in a TLC tank containing a solution of ethyl acetate/methanol/ammonium hydroxide (85/10/5). The first plate was heated and sprayed with a ninhydrin solution (0.1% in isopropyl alcohol) and placed under long wave ultraviolet (UV) light for 1 min. A pink spot developed at 2 cm.

The second plate was heated and sprayed with Dragendorff spray followed by a solution of 5% cupric chloride. A dark-brown spot developed at 3 cm and a light-brown spot at 2 cm. A third spray of 5% sodium nitrite followed the Dragendorff and cupric chloride sprays and both spots became dark brown.

Gas Chromatography–Mass Spectroscopy

The extracts were then analyzed using a Finnegan model 4000 GC-MS, with a 30-m DB-5 fused silica capillary column. The instrument conditions were as follows: detector temperature—92 C°; injector temperature—220 C°; column progressive temperature—170 to 260 C° by 20°C per minute (hold 11 min); column flow—20 mL/min; and transfer line temperature—260 C°. The compound had a retention time on this column of 4.16 min using these conditions (Fig. 2).

High-Pressure Liquid Chromatography

One millilitre of sample was extracted at pH 8.8, together with one millilitre of internal standard solution, into ten millilitre of chloroform/isopropyl alcohol (96/4). This extract was taken to dryness and reconstituted with 100 μL of methanol. Of the solution, 20 μL were injected onto an 8-mm by 10-cm resolve CN RADIAL-PAK cartridge, 10-μm particle size (Waters Z-module). Standard solutions varying from 1.6 to 40 mg/L in concentration of tocainide were analyzed along with the samples. Whole blood samples supplemented with 8 and 16 mg/L were also prepared and analyzed with the samples. The internal standard was a 10-mg/L solution of lidocaine. The following instrument conditions were used: flow—3 mL/m; wavelength—230 nm; and liquid phase—0.1*M* potassium phosphate monobasic (KH2P04)/ 0.02*M* tetramethyl ammonium chloride (TMA) 75%, methanol 25%.

Results

The mass spectrum of the compound detected qualitatively by thin-layer chromatography was identified as tocainide (Fig. 3). Analysis of various bodily fluids revealed levels as listed in Table 1.

Discussion

Following the discovery or markedly elevated levels of tocainide in the bodily fluids of the decedent, an investigation was undertaken to find the source of the medication. Ultimately, it was ascertained that the drug had been prescribed to her brother, who had undergone open heart surgery several years earlier. However, the medication containers were never located.

Tocainide was synthesized over a decade ago as part of a program to identify a lidocaine analog which had antiarrhythmic activity when given orally, a long duration of action, and a large therapeutic-toxic ratio [*2*]. The approved usage indications are for treatment of symptomatic ventricular arrhythmias. Tocainide does not undergo degradation upon passage through the bowel wall, nor first-pass hepatic elimination (as does lidocaine). About 40% of an oral dose is excreted unchanged in the urine, with the remainder degraded by the liver, up to 25% as a glucuronide [*3*]. These metabolites are inactive pharmacologically. The mean plasma half-life is 13 h in normal volunteers, varying from 9 to 37 h in patients with cardiac disease [*4*]. The usual dosage of tocainide is 400 to 600 mg, two to three times per day. The therapeutic range for serum concentrations is 4 to 10 mg/L, with 70% suppression of ventricular premature beats at 6 mg/L, and 90% suppression at 10 mg/L [*5*]. Toxicity is generally apparent at levels above 10 mg/L.

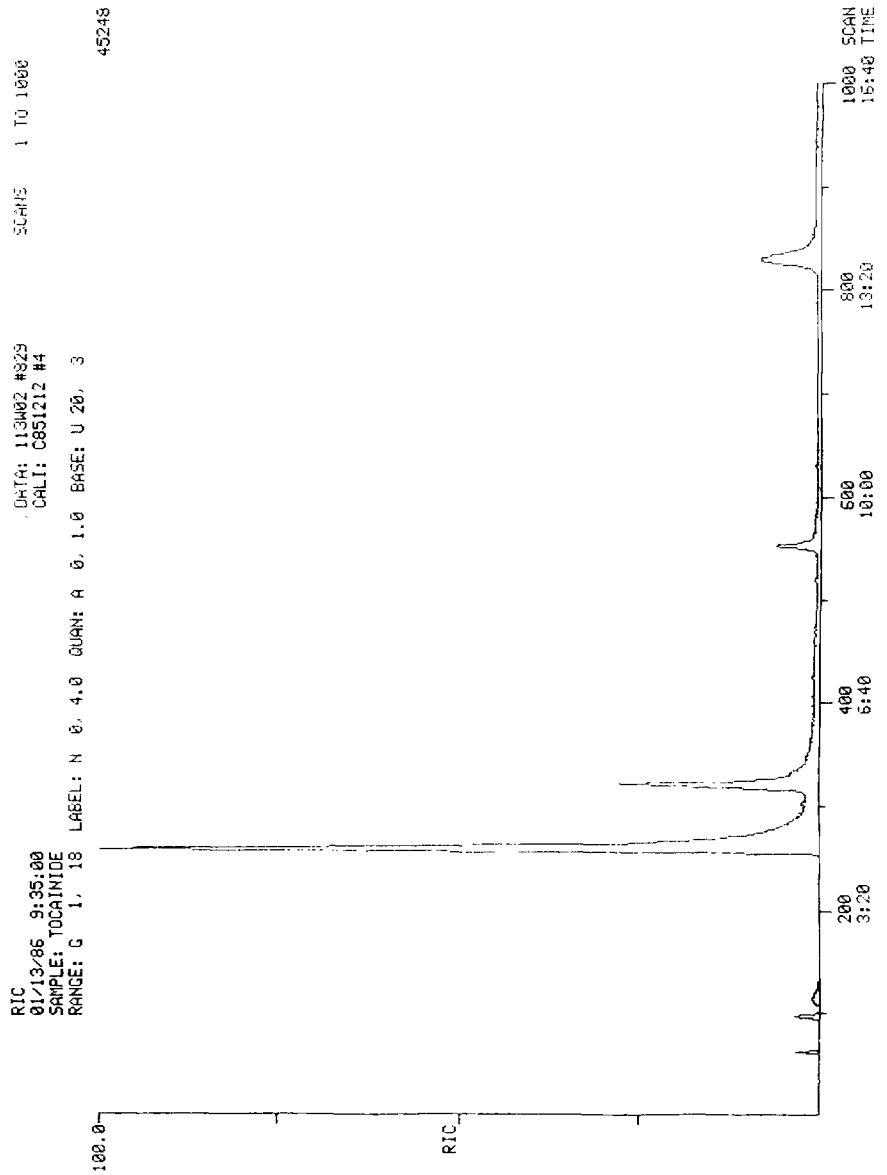

FIG. 2—*Gas chromatographic extraction of tocainide. Retention time was 4.16 min.*

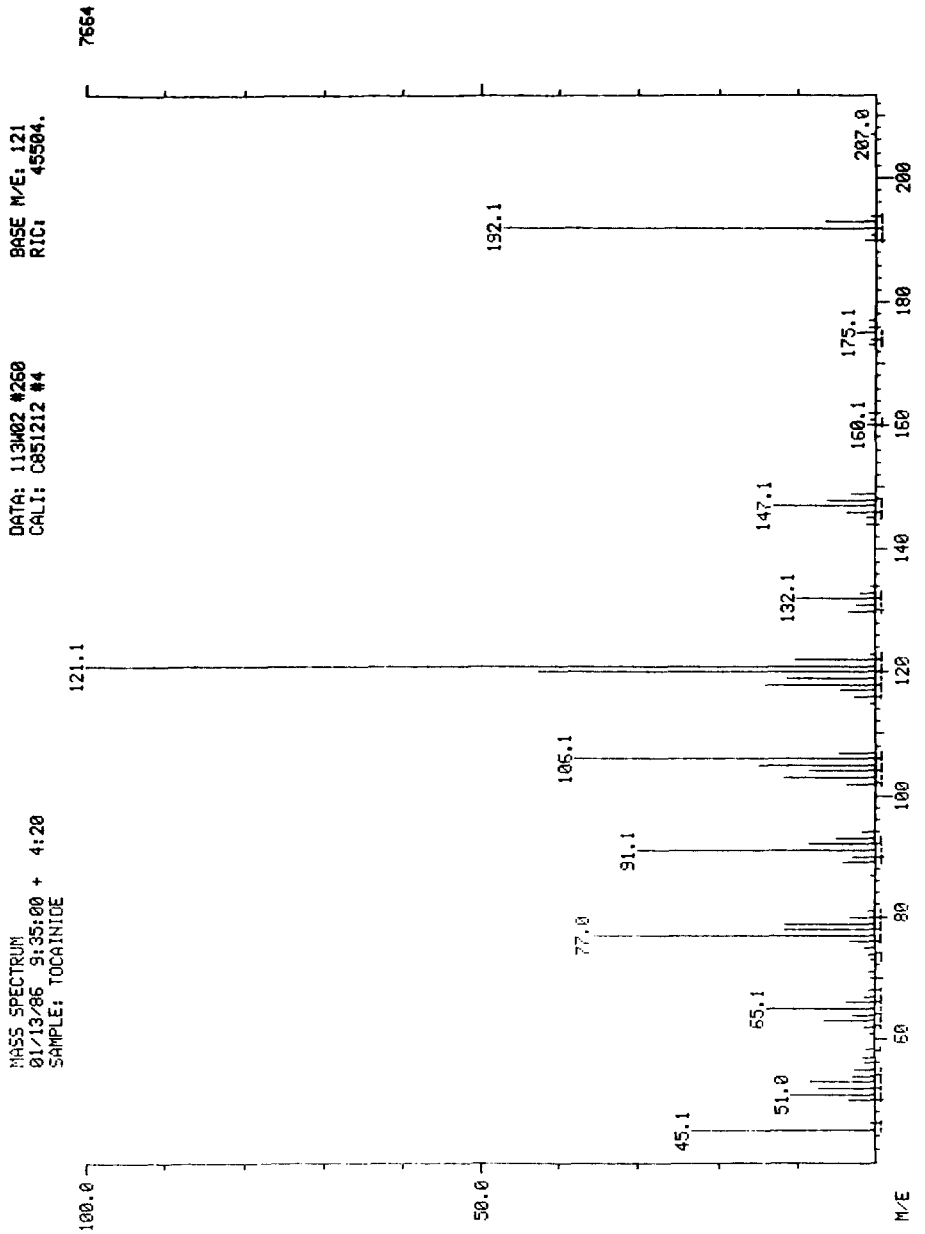

FIG. 3—*Mass spectrum of tocainide.*

TABLE 1—*Tocainide concentrations in bodily fluids obtained in Emergency Room immediately prior to death and at autopsy examination.*

Body Fluid	Tocainide Concentration, mg/L
Blood (antemortem)	78
Serum (antemortem)	68
Bile	11
Vitreous	9.3
Urine	(not available)

In the case presented here, a serum level of 68 mg/L was detected in an antemortem specimen, obtained during her attempted resuscitation. This is nearly seven times the upper limits of the recommended therapeutic levels. Although no human fatal toxicologic values have been reported to date, death with convulsions and apnea invariably occur in dogs following intravenous tocainide administration of 100 mg/kg [*6*]. Chronic high dose administration to rhesus monkeys revealed that lethal toxicity was primarily of central nervous system origin. The drug clearly is detectable in human vitreous, as shown in this case, but at a level 14% that of the serum. Because other cases of fatal tocainide overdosage will inevitably occur over the course of time, accumulation of human body fluid level data will more clearly characterize the distribution and toxicity parameters of this drug.

The adverse effects of tocainide therapy are predominantly related to the central nervous system (CNS) or gastrointestinal tract. A plethora of symptoms may develop, including nausea, vomiting, dizziness, tremor, and confusion, and as many as 20% of patients may discontinue chronic therapy because of side effects. Of the more serious adverse reactions, rare occurrences of coma, seizures, ventricular fibrillation, respiratory arrest, and pulmonary edema are of potential importance as a possible cause of death related to tocainide usage. Interestingly, agranulocytosis and bone marrow depression occur in 0.18% of patients, and occasional deaths have been reported as a result of this adverse reaction. This has prompted severe curtailment of recommendations for prescribing tocainide in the United Kingdom [*1*].

The predominance of potential CNS adverse reactions would suggest that the mechanism of death in tocainide overdosage is directly related to CNS toxicity. The clinical presentation in the case described here coupled coma with a ventricular tachyarrhythmia. An arterial blood gas performed upon her admission to the Emergency Room disclosed a pH of 6.67; this was soon corrected to 7.25 with bicarbonate administration, but with persistent ventricular fibrillation, progressing to asystole and electromechanical disassociation. Extremely high levels of tocainide may have a primary effect on the myocardium, with development of acidosis, in addition to direct CNS toxicity. As more cases of tocainide overdosage occur, a better definition of the specific toxic effects of this drug will be delineated in survivors, with probable concomitant development of effective emergency treatment protocols.

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