CASE REPORT

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Unsuspected Self-Poisoning With Flecainide and Alcohol

REFERENCE: Sadler, D. W. and Quigley, C., **"Unsuspected Self-Poisoning with Flecainide and Alcohol,"** *Journal of Forensic Sciences*, JFSCA, Vol. 40, No. 5, September 1995, pp. 903–905.

ABSTRACT: The death of a 23-year-old man by suicidal flecainide and alcohol poisoning is reported. Flecainide was identified by ultraviolet (UV) spectrophotometry and gas chromatography-mass spectrometry (GC-MS). Flecainide levels, quantitated by high performance liquid chromatography (HPLC) with UV detection were: femoral blood 7.3 mg/L, urine 117 mg/L, stomach contents 19 mg and liver 302 mg/kg. Ethanol levels in femoral blood, urine and vitreous humor were 107, 136 and 113 mg%, respectively. The importance of carefully considering all the available pathological and toxicological data, together with the past medical history and circumstances surrounding the death in poisoning cases is emphasized.

KEYWORDS: toxicology, poisoning, flecainide, redistribution

The interpretation of toxicological levels of new drugs such as flecainide is often a problem. Flecainide (Tambocor^{R}) is a class 1c antiarrhythmic drug used to treat ventricular arrhythmias. Its major electrophysiological action is sodium channel blockade, causing a dose-related decrease in intracardiac conduction velocity, slowed cardiac cell depolarization and a negative inotropic effect. Adverse effects include a negative inotropic effect, depression of cardiac conduction, ventricular tacharrhythmias and severe bradycardia [*1*]. Its half life averages 13 to 20 h [*2*], the therapeutic range in serum is 0.2 to 0.8 mg/L [*3*], the volume of distribution (VD) is 5 to 13.4 L/kg [*3*] and it exhibits significant (37 to 58%) serum protein binding [*4*].

Case History

The deceased was a 23-year-old white male who had been on medical treatment with various drugs for Wolff-Parkinson-White Syndrome (WPWS) since the age of 11 years. Eight months prior to death he underwent radiofrequency ablation therapy of an accessory antero-septal conduction pathway. Shortly after this his palpitations recurred and he was commenced on Flecainide therapy (100 mg tds). On the night of his death he requested a female friend to visit him. She was concerned about his apparent depressed state of mind and made three further visits that evening. On her third visit he complained of a sore stomach, was unsteady on his feet and vomited. This she attributed to his reported alcohol consumption prior to her arrival and she helped him onto his bed where he lay face down until she left. On her fourth visit she found him in the same position, blue and gasping for breath but he was dead when the ambulance arrived a short time later. At this time a drug overdose was not suspected and the investigating police officer found no suicide note or empty medication containers within the house. The case was presented for autopsy as a suspected natural death. Prior to autopsy, further enquiries to his general practitioner disclosed that he had been depressed about the perceived failure of ablation treatment for WPWS and had lost his job ten days prior to death.

Received for publication 27 Dec. 1994; revised manuscript received 27 Feb. 1995; accepted for publication 28 Feb. 1995.

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Autopsy Findings

The body weighed 50 kg and had been refrigerated at 4°C for 3 days prior to autopsy. There were no features of decomposition. The heart (350 g) exhibited three smooth, oval white scars up to 8 mm in diameter on the endocardium of the right atrium and ventricle, in keeping with previous radiofrequency ablation therapy. The stomach contained 50 mL of turbid reddish-brown fluid. Autopsy was otherwise unremarkable.

Toxicological Analyses

Chemicals and Reagents

Flecainide was obtained from 3M Company. All other reagents were of "Analar" or HPLC grade.

Screening

Ethanol analysis was performed on blood, urine, and vitreous humor samples using headspace analysis with a Perkin Elmer HS101 autosampler and Perkin Elmer 8500 Gas Chromatograph.

Routine drug screens on liver and blood proved positive for flecainide. Flecainide was identified using UV spectrophotometry and gas chromatography-mass spectrometry on a liver extract. No other drugs were detected.

Basic Drug Screen on Liver

Approximately 30 g of liver were homogenized with an equal volume of distilled water, made alkaline with 60% potassium hydroxide and extracted with diethyl ether. The ether was washed with distilled water and then extracted into 0.1 N sulphuric acid. The acid extract was read on a Cecil 5000 scanning UV spectropho-

tometer between 190 nm and 360 nm. The acid extract was then extracted into chloroform after making alkaline with 10% sodium hydroxide. The organic extract was evaporated to dryness at 60°C under a stream of dry nitrogen, reconstituted in methanol and analyzed using a Perkin Elmer 8500 GC coupled to an Perkin Elmer Ion trap detector.

UV maximum of flecainide: 295 nm

Major ions: mz 84, 107, 209, 237, 381.

Quantitation

Fifteen g of liver were homogenized with distilled water to a final volume of 90 mL and then diluted 1 to 10 with distilled water. Stomach contents were homogenized and diluted 1 to 100 with distilled water. Urine was diluted 1 to 25 mL.

One mL of blood, diluted urine, stomach or liver homogenates were extracted based on the method of Forrest et al. [*3*] using 50 μL of 100 μg/mL clomipramine as internal standard. HPLC with UV detection was used for quantitation of the extracts.

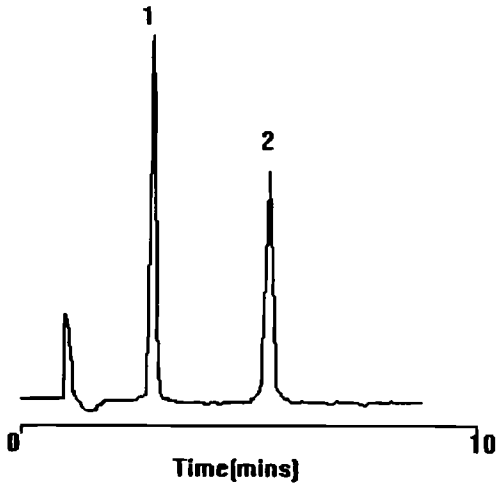
HPLC Conditions

Room temperature (20°C). Column: 15 cm Hypersil ODS analytical column with a 2 cm guard column. Mobile phase: 300 mL of 0.01 M di-sodium hydrogen phosphate, 200 mL of acetonitrile and 0.6 mL of n-nonylamine buffered to pH3; Flow rate: 1 mL/min; Wavelength: 295 nm.

Results

A standard curve over the range 1 to 10 μg/mL was linear with a correlation coefficient of 0.9993. Figure 1 represents the HPLC trace.

Measured flecainide levels were: femoral blood 7.3 mg/L, urine 117 mg/L, liver 302 mg/kg and stomach contents 376 mg/L (equivalent to 19 mg in 50 mL of total stomach contents). Measured ethanol concentration were: femoral blood 107 mg%, urine 136 mg% and vitreous humor 113 mg%.



HPLC of blood extract

1. Flecainide
2. Internal standard (Clomipramine)

FIG. 1

TABLE 1—*Flecainide levels, blood alcohol concentrations (BAC) and post mortem interval (PMI) in 3 fatal flecainide poisonings.*

	Flecainide Conc. (mg/L)			Stomach	BAC	PMI
	Blood	Liver	Urine	(mg)	(mg%)	(h)
Present case	7.3[a]	302	117	19mg[c]	107	60
Forrest [*3*]	16.3[a]	111	–	426 mg[d]	0	24
Levine [*2*]	13[b]	180	54	120mg	0	–

[a]blood sample milked from femoral vein.
[b]heart blood sample.
[c]corresponds to 376 mg/L of stomach contents (50 mL collected).
[d]corresponds to 4260 mg/L of stomach contents (100 mL collected).

Table 1 compares our measured levels with those of two other reported fatalities involving flecainide [*2,3*].

Discussion

This case illustrates the importance of considering the background circumstances and medical history in the detection of self-poisoning cases. Where background information is scanty and potentially lethal natural disease exists there is a danger of attributing death to the natural disease without considering the possibility of self-poisoning. The presence of a suicide note or empty medication bottles at the locus and tablet debris in the stomach at autopsy cannot solely be relied upon to indicate the need for toxicological analyses. In this case, the recent medical and social history and the circumstances surrounding the death provided the only evidence to suggest the possibility of self-poisoning.

In view of the sampling site and postmortem interval in this case, it was suggested by the drug company that the flecainide levels in femoral venous blood may have been artefactually elevated by postmortem redistribution from solid organs, possibly including skeletal muscle[3,4] [*3*]. This suggestion is based on flecainide having a high volume of distribution, a property that implies significant tissue binding and makes postmortem drug redistribution likely [*3,5*]. However, because cardiac and central blood specimens are prone to contamination by post mortem drug diffusion from the nearby liver and stomach [*5,6*], femoral blood is the preferred specimen for most quantitative drug analyses. It is of more practical interest here that Levine raised the possibility of flecainide diffusion from liver to cardiac blood [*2*].

The flecainide levels measured in our case are broadly similar to those in two other reported fatal flecainide poisonings (Table 1). The presence of higher levels in liver and urine, together with lower levels in femoral blood and gastric contents in our case would tend to support the circumstantial evidence that death likely occurred several hours after ingesting the drug. While flecainide may accumulate in the liver following therapeutic use, measured hepatic levels in our case are particularly high (Table 1).

It has been suggested that alcohol may have a protective action in flecainide poisonings [*1*]. However, in our case coexisting alcohol intoxication resulted in death at lower blood flecainide levels than those in two fatalities not associated with alcohol intoxication [*2,3*].

Taken as a whole, the medical history, circumstances, autopsy and toxicological findings in this case point to fatal self-poisoning with flecainide and alcohol.

[3]Copy of communication between Information Scientist, 3M Health Care Limited, Loughborough, England and Dr. Forrest (Royal Hallamshire Hospital, Sheffield) 1989.

[4]Medical Director, 3M Health Care Limited, Loughborough, England (personal communication) 1992.

Acknowledgment

We wish to thank Professor D. J. Pounder for his helpful comments during the preparation of this manuscript.

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