CASE REPORT

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A Carpipramine Related Fatality

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ABSTRACT: A fatality following ingestion of the tricyclic antidepressant carpipramine (Prazinil®) and ethyl alcohol is described. Carpipramine was quantitated by high performance liquid chromatography. The concentration of carpipramine was 2.0 mg/L in blood and 0.44 mg/L in urine. Ethyl alcohol was measured by headspace gas chromatography and found to be 105 mg/dL in blood and 55 mg/dL in the urine. Quantitative analysis of stomach contents was positive for carpipramine by thin-layer chromatography. To our knowledge, this is the first reported fatality involving carpipramine.

KEYWORDS: pathology and biology, carpipramine, death, chromatographic analysis

Carpipramine dihydrochloride is a tricyclic antidepressant first synthesized and marketed in Japan[3] in 1965. In 1970, carpipramine (Prazinil®) was introduced in France by Specia, Paris, France.

The chemical structure (Fig. 1) is similar to imipramine with a side chain piperidinocarbamide-piperidine analogous to certain butyrophenones. Pharmacologically, the compound has both antidepressant and neuroleptic activity [*1-7*]. It is prescribed for the treatment of endogenous depression, schizophrenia, and psychotic disorders.

Several recent reports summarize fatal and nonfatal intoxications for the most common tricyclic antidepressants [*8-11*]. However, only 2 reports in the French literature [*12,13*] involving nonfatal intoxications with carpipramine have been published. The first report of 26 cases reported to the Poison Control Center in Paris described the cardiotoxic symptoms seen in overdoses but no drug concentrations were measured in blood or urine. The second report involving one case emphasized appropriate treatment when ventricular tachycardia was seen. All 27 patients discussed in these studies survived. No information on carpipramine related fatalities was provided by Yashitomi Pharmaceutical Industries (Japan) or Specia (France). This report documents analytical findings in blood and urine of carpipramine and ethyl alcohol in a single case of death.

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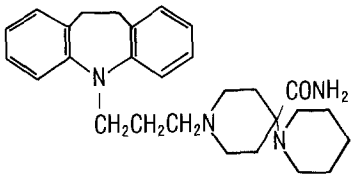

CARPIPRAMINE

FIG. 1—*Chemical structure of carpipramine.*

Case History

A male French citizen visiting Canada was found dead. Investigation at the scene revealed an empty container of carpipramine (Prazinil®) which was prescribed at 50-mg t.i.d.

An autopsy was not performed. Toxicologic analysis on stomach contents, blood, and urine are described below. Pill fragments were found in the stomach.

A mixed drug overdose was considered the cause of death.

Toxicologic Analysis

Standards and Reagents

Acetonitrile and methanol were high performance liquid chromatographic (HPLC) grade and glass distilled (Caledon Laboratories Ltd., Georgetown, Ontario). Carpipramine dihydrochloride monohydrate was supplied by Yoshitomi Pharmaceutical Industries, Ltd. Osaka, Japan and Specia, Paris, France. The internal standards clomipramine hydrochloride and clocapramine dihydrochloride were obtained from Ciba-Geigy, Mississauga, Ontario, and Yoshitomi, Osaka, Japan, respectively.

Thin-Layer Chromatography

Drug screening on urine and stomach contents was performed by thin-layer chromatography (TLC). The specimen was made basic with sodium carbonate (pH 8.5) and mixed with chloroform. The chloroform layer was dried under nitrogen. After drying, the residue was dissolved in chloroform : methanol (1 : 1) and spotted on a silical gel 60 plate (E. Merck and Co., Darmstadt, W. Germany). After developing in a tank saturated with ethyl acetate : methyl alcohol : ammonium hydroxide (170 : 20 : 10), one side of the plate was sprayed with iodoplatinate reagent and the other side with Forrest reagent [*14–16*].

Gas Liquid Chromatography

Ethyl alcohol quantitation was performed as reported previously [*17*].

High Performance Liquid Chromatography

Liquid chromatography was performed on a Model 740 solvent delivery system by Spectra Physics, SF 770 variable wavelength ultraviolet (UV) detector by Schoeffel Instruments and an Omniscribe recorder by Houston Instruments (all obtained from Technical Marketing Associates, Halifax, Nova Scotia). Analysis was performed at ambient temperature using a 250- by 4.6-mm RP-8 column with 5-μm particle size (Brownlee Labs, Santa Clara, CA). Detector wavelength was set at 205 nm.

The mobile phase for carpipramine was a buffer solution consisting of 0.01 mol/L of potassium dihydrogen phosphate mixed with acetonitrile and *n*-nonylamine (550/450/0.6). This mixture was adjusted to pH 3.2 with phosphoric acid. The flow rate was 1.6 mL/min.

Clomipramine and clocaprimine were used independently as internal standards. Stock

drug solutions at 50 μg/mL (as free bases) were prepared in methyl alcohol. A drug free serum was added to give a stock standard of 1500 ng/mL of carpipramine free base. To a 2.0 mL of sample (standard and unknown) 5 mL of hexane:isoamyl (97:3) was added containing the internal standard (200 ng/mL) and 0.1 mL of saturated sodium carbonate. The tubes were mixed for 20 min and centrifuged. The organic extract was transferred to a 8.0-mL screw cap tube with a plastic pasteur pipette. A 0.1-mL mixture of mobile phase:0.1*M* phosphoric acid (1:1) was added followed by vortexing and then centrifugation. The organic layer was aspirated to waste and the aqueous phase (30 μL) injected onto the HPLC column. The range was set at 0.02 absorbance units full scale.

Peak height ratios were used to calculate drug concentrations using the average factor obtained from the two internal standards. Concentrations of carpipramine were within 10% of each other using the carpipramine analog clocapramine as internal standard or clomipramine.

Both previously reported methods for carpipramine analysis in dog serum used normal phase HPLC with a silica column [*18,19*].

Results

Qualitative analysis of the stomach contents were positive for carpipramine. Urine drug screening gave a TLC pattern consistent with an imipramine overdose (parent drug and several metabolites seen with the Forrest reagent and iodoplatinate spray).

A summary of the quantitative results appears in Table 1.

Chromatograms of the blood extract for carpipramine are found in Figs. 2 and 3.

Discussion

No information on serum concentrations of carpipramine, when given in usual therapeutic dosages (50 to 400 mg/day) or after an overdose, were found in a literature search or through correspondence with the two drug companies. In pharmacokinetic studies in dogs, however, the average peak concentration was 250 and 500 ng/mL when receiving 75 and 150 mg of carpipramine orally [*19*].

In a clinical study investigating schizophrenia, a favorable clinical response was seen with 50- to 400-mg/day doses [*2*]. Waggon [*6*] compared carpipramine with doxepin in 46 patients including depression, schizoaffective disorders, and paranoid schizophrenia. All patients received 100 mg t.i.d. Using the Hamilton rating scale and other indices for assessment, the antidepressant and antipsychotic effects of carpipramine were demonstrated.

Perier [*20*] and Deniker [*3*] reported that carpipramine has antidepressant and neuroleptic activity pharmacologically. In overdose cases, clinical features resembled other tricyclic antidepressant ingestions including anticholinergic effects and cardiotoxicity. Activity as a neuroleptic agent was shown in animal studies by assessing binding affinity of carpipramine to the haloperidol receptor in rat striatal synaptosomes. Carpipramine affinity was equal to chlorpromazine and 100 times stronger than imipramine binding to this receptor [*1*].

No information was obtained on human metabolism of carpipramine. Using tritium labelled carpipramine in rats [*21*], 3% of the radioactivity was excreted in the urine and 80%

TABLE 1—*Summary of toxicological analysis.*

	Specimen Concentrations	
Drug	Blood	Urine
Carpipramine, mg/L	2.0	0.44
Ethyl alcohol, mg/dL	105	55

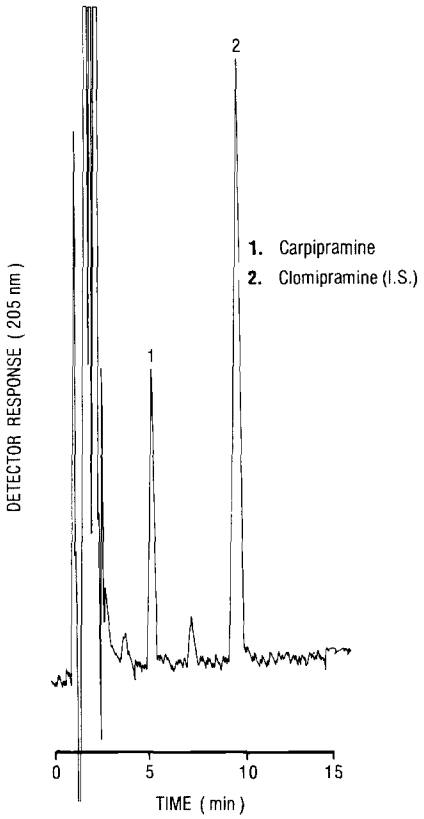

FIG. 2—*High performance liquid chromatogram of blood extract:* (1) *carpipramine 2.0 mg/L and* (2) *clomipramine internal standard.*

in feces by 72 h. Analysis after enzymatic hydrolysis indicated that glucuronide conjugates are formed.

Two reports involving 27 overdose cases [*12,13*] primarily discussed the side effects and treatment. Unfortunately, no blood measurements were obtained in any of these cases.

Animal toxicity studies [*5*] in mice, rabbits, and dogs initially showed a state of palsy in hind limbs followed by tremor, convulsions, cyanosis, and respiratory paralysis leading to death. Since no human toxicity data were available, acute toxicity studies in rats and mice for carpipramine and imipramine are found in Table 2 [*5*]. By certain routes of administration, there are comparable results with imipramine. By the oral route, however, carpipramine toxicity is significantly different than imipramine in these two animal species.

Carpipramine in blood was 2.0 mg/L in this case. Cardiac and respiratory toxicity leading to death have been associated with total tricyclic antidepressant concentrations (parent and desmethyl metabolite) of greater than 1.0 mg/L. In this case, the blood carpipramine and ethyl alcohol concentrations were both much higher than the urine values. These findings are consistent with the investigational impression of a short time interval between drug ingestion and death.

In summary, it is felt that the major factor in this fatality was carpipramine. The contribution of ethyl alcohol may be significant as a result of possible synergistic action between the drug and ethyl alcohol.

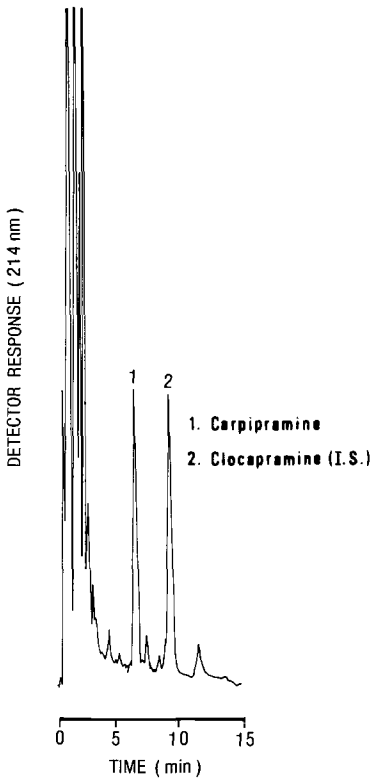

FIG. 3—*High performance liquid chromatogram of blood extract:* (1) *carpipramine 2.0 mg/L and* (2) *clocapramine internal standard.*

TABLE 2—*Acute toxicity summary* [5].

Animal	Route of Administration	Mean LD_{50}, mg/kg	
		Carpipramine	Imipramine
Mice	i.v.	28.2	32.2
	i.p.	136.0	106.0
	s.c.	>4000	262
	oral	2180	550
Rats	i.v.	37.0	21
	i.p.	76.0	72
	s.c.	>2500	217
	oral	1025	502

[a]i.v. = intravenous, i.p. = intraperitoneal, and s.c. =subcutaneous.

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