*Case Report*

# A Fatal Case of Alimemazine Poisoning

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## Abstract

**Alimemazine, a phenothiazine derivative with the properties of antihistamines, was determined by a selective high-performance liquid chromatographic technique in blood and tissues from a postmortem case. The blood concentration of alimemazine was 6.52 µg/mL. The brain was the major site of drug deposition, and tissue distribution is discussed in light of the existing literature.**

## Introduction

Alimemazine or timeprazine (*N,N*-dimethyl-2-methyl-3-[phenothiazin-10-yl] propylamine) (Figure 1) is a phenothiazine derivative related to chlorpromazine; it has the properties of antihistamines. It has been marketed in France since 1958 under the name Théralène® (Theraplix Laboratories) and is used mainly for its marked effect in the relief of pruritus. The drug has pronounced sedative and antihistamine effects and some antimuscarinic actions. Alimemazine may also be used as a cough suppresser. The usual daily dose is 5–40 mg orally (1).

Fatal overdoses due to alimemazine have not been previously reported, as deaths due to phenothiazines seem to be exceptional; however, some cases have been published, which include overdoses of cyamemazine (2), trifluoperazine (3), thioridazine (4), and chlorpromazine (5–7).

We present here a fatality in which alimemazine was identified in blood using a screening procedure based on high-performance liquid chromatography with diode-array detection (HPLC–DAD) and then quantitated in postmortem samples by routine HPLC.

## Case History

A 58-year-old male, pensioned and suffering from clinical depression, was found dead at home lying on his bed. Several empty blisters of Théralène (alimemazine, 5-mg tablets) were found near his bed. Autopsy findings were unremarkable, and they showed no evidence of violence. No samples were taken for histology.

The following postmortem samples were taken for toxicological analysis: femoral blood, urine, gastric contents, bile, liver, muscle (psoas), brain, kidney, and heart.

## Experimental

### Materials

Methanol, tetrahydrofuran, chloroform, 2-propanol, *n*-heptane, and acetonitrile were HPLC grade (Merck, Germany). All other chemicals and reagents were analytical grade (Merck and Prolabo, France). Prochlorperazine dimaleate was obtained from Spécia Labs. (France). Alimemazine tartrate was a gift of Rhône–Poulenc Labs. (France).

### Instrumentation

*Drug screening.* The HPLC–DAD system consisted of a pump (Waters 600E), a 200-µL loop volume automatic sample injection module (Waters 715 Ultra Wisp), and a UV–vis diode-array

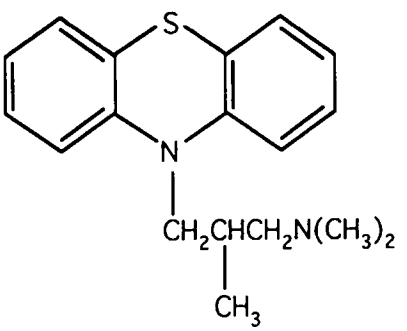


**Figure 1.** Chemical structure of alimemazine.

spectrophotometer (Waters 991); the wavelength range, the resolution, and the sampling interval were set at 200–400 nm, 1.3 nm, and 1 spectrum/s, respectively. The column was a 4-µm NovaPak $C_{18}$ column (300 × 3.9-mm i.d.) (Waters), which was thermostated at 30°C during all experiments. Elution was performed isocratically (flow rate, 0.8 mL/min; average pressure, 19.65 MPa), and a mobile phase of methanol, tetrahydrofuran, and $10^{-2}$M $KH_2PO_4$ buffer (pH 2.6) (65:5:30, v/v/v) was used. Under these operating conditions, the limit of detection for alimemazine was approximately 60 ng/mL.

*Alimemazine quantitation.* Alimemazine was quantitated by a previously described routine HPLC method (8) using a 5-µm Spherisorb CN column (250 × 3.2-mm i.d.) (Interchim, France) operated at ambient temperature (19–22°C). A mobile phase of acetonitrile and a 0.015M $CH_3COONa$–$CH_3COOH$ buffer (pH 6.5) (95:5, v/v) were used. The flow rate was 1.0 mL/min, and spectrophotometric detection occurred at 254 nm. For alimemazine in whole blood ($n$ = 3), the method was linear over the range of 0.04–20.00 µg/mL ($y$ = 1.98$x$ – 0.07, where $y$ = alimemazine concentration in micrograms per milliliter and $x$ = area of alimemazine area of the internal standard prochlorperazine); the limit of detection was 20 ng/mL.

For each other medium (fluid or tissue), the accuracy of the procedure was tested at 1 µg/mL or 1 µg/g. Coefficients of variation ranged from 4 to 13% in the assay.

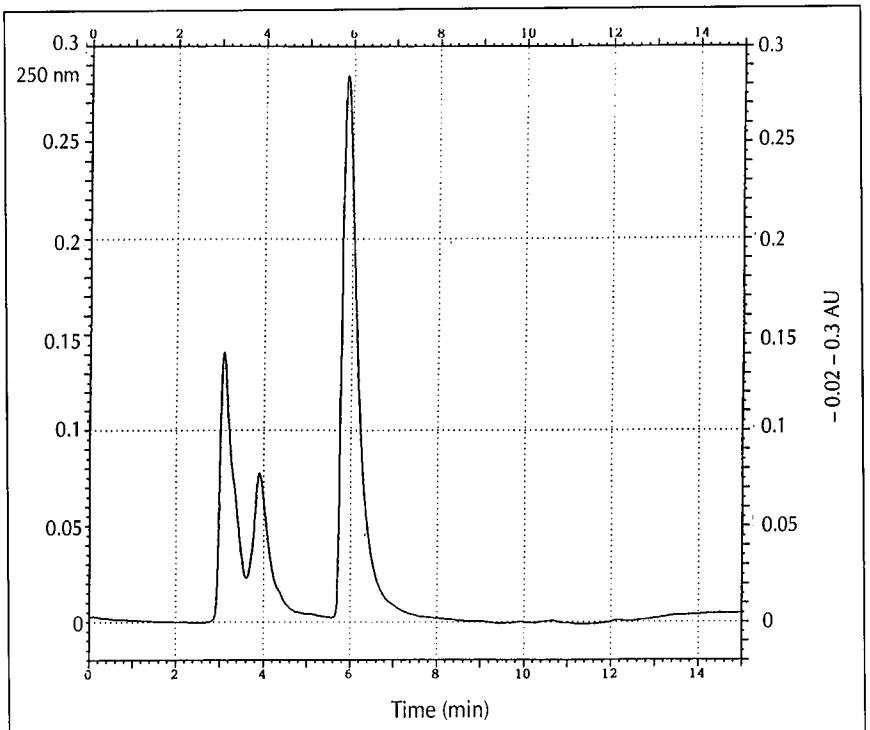


**Figure 2.** Typical chromatogram obtained during the screening procedure of the whole blood specimen. The peak at 3.09 min is an endogenous compound. Alimemazine eluted at 5.87 min; the concentration was 6.52 µg/mL. The peak at 3.90 min is a metabolite of alimemazine.

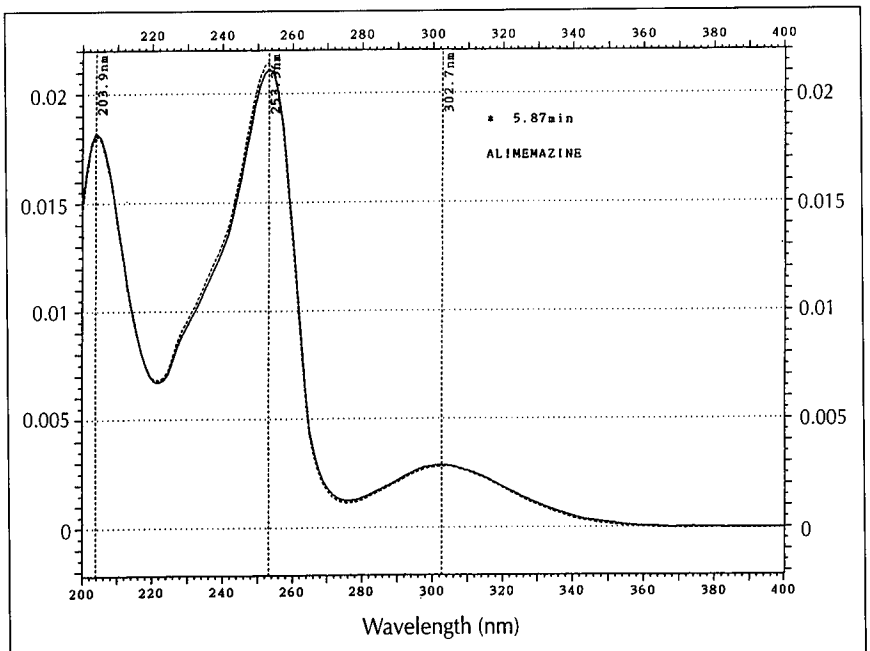


**Figure 3.** UV spectra (200–400 nm) of alimemazine (full line) and alimemazine from the library (dotted line); similarity, 989/1000. Resolution, 1.3 nm.

## Procedure

*Drug screening.* To 2.0 mL postmortem blood in a 15-mL centrifuge tube were added 5.0 mL chloroform–2-propanol–*n*-heptane (60:14:26, v/v/v) and 1.5 mL saturated $NH_4Cl$ (pH 9.5) buffer solution. After horizontal agitation (10 min) and centrifugation (10 min at 2800 × $g$), the lower organic phase was removed and evaporated at 45°C in a rotary evaporator (Speed Vac concentrator A290; Savant Instruments). The residue was dissolved in 100 µL of the eluent, and 50 µL was injected into the HPLC–DAD system. Concurrently, fluorescence polarization immunoassay screening of the blood and urine samples was performed using the Abbott ADx™ analyzer with the following assay kits: benzodiazepines and barbiturates (blood and urine), tricyclic antidepressants, salicylates and paracetamol (blood), opiates, cocaine, cannabinoids, and amphetamine and methamphetamine (urine). In addition, the blood sample was assayed for meprobamate by gas chromatography (GC)–flame ionization detection and for ethanol and organic solvents (i.e., methanol, acetonitrile, acetone, 2-propanol, diethylether, methylene chloride, carbon disulfide, methyl *tert*-butylether, chloroform, ethyl acetate, tetrahydrofuran, benzene, toluene, and trichloroethylene) by headspace GC.

*Alimemazine quantitation.* To 1.0 mL postmortem fluids or tissue homogenates

($^1/_4$ part tissue for three parts deionized water, w/w) were added 5.0 mL *n*-heptane–isoamyl alcohol (98.5:1.5, v/v), 500 µL of a pH 8.5, saturated $Na_2CO_3$ buffer solution, and 20.0 µL of a 100-µg/mL methanolic solution of prochlorperazine (internal standard). After agitation and centrifugation, the organic supernatant was evaporated to dryness. The dry extract was then dissolved in 100 µL acetonitrile, from which 70 µL was injected onto the Spherisorb CN column. Quantitation was achieved for each sample by comparing peak-area ratios (alimemazine to the internal standard) with the previously stored specific calibration curve. All the standards were prepared on the day of analysis.

## Results and Discussion

The HPLC–DAD screening indicated the presence of alimemazine (Figures 2 and 3). No other pharmaceuticals or drugs of abuse were identified.

**Table I. Alimemazine Concentrations in Postmortem Samples**

| Sample | Concentration (µg/mL or µg/g) |
|---|---|
| Femoral blood | 6.52 |
| Urine | 6.22 |
| Bile | 4.44 |
| Gastric contents | 80.19 |
| Brain | 19.90 |
| Liver | 18.69 |
| Kidney | 19.13 |
| Heart | 16.62 |
| Muscle | 1.43 |

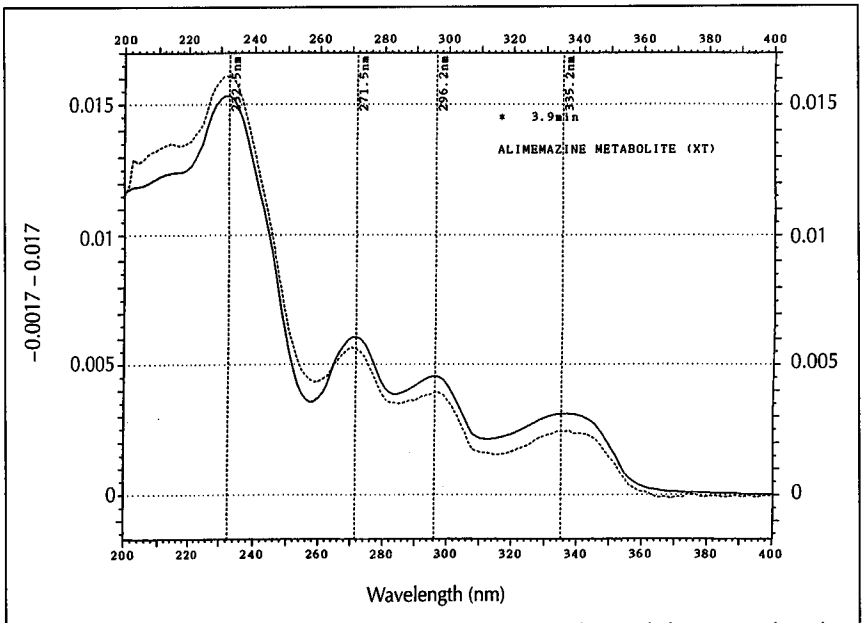


**Figure 4.** UV spectra (200–400 nm) of alimemazine sulfoxide (full line) and alimemazine from the library (dotted line); similarity, 946/1000. Resolution, 1.3 nm.

Alimemazine was detected in all the autopsy samples. Concentrations are presented in Table I.

Acute intoxications with phenothiazines are not rare, but fatalities seem to be exceptional; by 1980, only approximately 15 deaths had been described in the American medical literature (9).

To date, no fatalities involving alimemazine (alone or in association) have been reported. For this reason, data concerning alimemazine poisoning are useful for presenting information on the concentrations of the drug in biological samples.

Following single oral doses of 5 mg to two subjects, peak plasma concentrations of 0.8 and 1.8 ng/mL were reported at 4 h (10).

In our case, the postmortem blood concentration exceeded approximately 10,000 times these values.

The highest tissue concentration was measured in the brain (19.9 µg/g), suggesting that this tissue may represent a sequestration compartment for phenothiazines. This is consistent with the marked lipophilic properties (9,10) and extremely slow elimination rates of these compounds. In other cases (6,7), phenothiazine concentrations in the brain were very high.

The distribution of phenothiazines in blood and liver varies considerably from case to case. In the present report, the liver concentration exceeded approximately three times the blood concentration. The reported liver-to-blood ratio in the literature ranged from 0.65:1 (2) to 60:1 (6).

However, considering the fact that phenothiazines undergo extensive hepatic metabolism and that most data on postmortem tissue concentrations have been obtained by means of UV spectrophotometric procedures that do not separate parent drugs from metabolites, it is believable that liver concentrations of unchanged phenothiazine have been, in numerous cases, overestimated.

It has been reported that alimemazine is essentially metabolized as sulfoxides and glucuronides. Alimemazine sulfoxide was detected in all the autopsy samples (Figure 4). Our analytical studies have not been able to evaluate the concentration of the metabolite because of the unavailability of primary reference material.

## References

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