CASE REPORT

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Toxicological Findings in a Death Resulting from the Ingestion of Trimipramine

REFERENCE: Meatherall, R. C., Guay, D. R. P., Nokes, J. M., and Keenan, J. R., **"Toxicological Findings in a Death Resulting from the Ingestion of Trimipramine,"** *Journal of Forensic Sciences*, JFSCA, Vol. 28, No. 4, Oct. 1983, pp. 1023-1029.

ABSTRACT: A fatality following ingestion of the tricyclic antidepressant trimipramine is presented. Whole blood concentrations of trimipramine and its metabolite *N*-desmethyltrimipramine were measured by gas-liquid chromatography and found to be 400 and 1130 ng/mL, respectively. These findings are compared to those of previous unpublished trimipramine fatalities and fatalities caused by other tricyclic antidepressants.

KEYWORDS: toxicology, death, trimipramine, tricyclic antidepressants

Trimipramine maleate (Surmontil®, Rhône-Poulenc Pharma Inc., Montreal, Quebec) is a potent and effective antidepressant which is used in the treatment of endogenous and exogenous depressions characterized by both agitation/anxiety and psychomotor retardation [*1*]. This agent is a relatively new drug to U.S. physicians, having been approved by the Food and Drug Administration only in late 1979. However, in most of the western world, this is an established drug with a 20-year history of clinical use. It is expected that its use will expand since studies demonstrating its efficacy in the treatment of peptic ulcer continue to appear [*2-7*]. Many cases of suspected fatalities caused by trimipramine ingestion have been reported to the manufacturers.[4] Based on the expanding spectrum of use, overdose with trimipramine will undoubtedly increase in the future.

No fatalities suspected to be secondary to trimipramine ingestion, which also document pertinent analytical findings on biological fluids, have been reported.

Received for publication 31 Jan. 1983; revised manuscript received 14 March 1983; accepted for publication 15 March 1983.

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Case Report

While at home, E. K., an obese 55-year-old white female had complained of dizziness. Her husband summoned an ambulance only after she collapsed unconscious to the floor. Upon arrival at hospital, she had been asystolic without cardiopulmonary resuscitation for at least 9 min. Resuscitation was successful with the use of 1 mL of epinephrine (1:1000), 50 meq of sodium bicarbonate, 200 mg of lidocaine by bolus, and DC countershock. Cardiac rhythm ranged from asystole to ventricular tachycardia and fibrillation to sinus rhythm. Past medical history elicited from the husband included a long history of rheumatism and depression; the latter condition being treated with trimipramine (Surmontil®) alprazolam (Xanax®) and pimozide (Orap®) the former condition being treated with zomepirac (Zomax®). Prescribed dosages were unavailable. On examination, no peripheral edema was noted, heart sounds were normal and the chest was clear. Soon after admission, she became hypotensive and the rhythm strip began to show frequent multifocal premature ventricular contractions. Dopamine and 2-mg/min lidocaine infusions were started and the patient was transferred to the Intensive Care Unit. Shortly thereafter, grand mal seizures began which were controlled with injections of diazepam, 800 mg of phenytoin, and 300 mg of phenobarbital. Arrhythmias continued, consisting of sinus tachycardia with 1° atrio-ventricular block, supraventricular tachycardia, and multifocal premature ventricular contractions in singlets and couplets. In spite of an upward titration in dopamine dosage, hypotension progressed to cardiogenic shock and anuria. Thirteen hours after admission, idioventricular rhythmm supervened with cardiac arrest and death.

Autopsy findings included bilateral pulmonary edema, mild arteriosclerotic heart disease, and evidence of early ischemic changes in the left posterior wall of the myocardium. Toxicological analyses of gastric fluid and blood are described below. The bladder was found empty.

Analytical Procedures

Materials

All solvents were high performance liquid chromatographic (HPLC) grade except chloroform which was pesticide grade (Fisher Scientific, Pittsburgh, PA). Trimipramine and *N*-desmethyltrimipramine as their maleate salts were obtained from Rhône-Poulenc Pharma Inc., Montreal, Quebec, Canada. Zomepirac was obtained as Zomax. Lidocaine hydrochloride was obtained as a 2.0% solution (Xylocaine®, Astra Pharmaceuticals Ltd., Mississauga, Ontario, Canada). Phenytoin powder was obtained from Parke-Davis and Co., Ltd., Scarborough, Ontario, Canada while phenobarbital powder was obtained from Winthrop Laboratories, Aurora, Ontario, Canada. Clomipramine hydrochloride powder was obtained from Ciba-Geigy, Mississauga, Ontario, Canada.

Thin-Layer Chromatography

Blood and gastric samples were initially subjected to a general drug screen by thin-layer chromatography (TLC). Ten millilitres of each were made acidic with 2 mL of 1*N* hydrochloric acid and shaken with 10 mL of chloroform. The chloroform was dried and the residue spotted twice on a silica gel thin-layer plate (Baker flex IB2-F, J. T. Baker Chemical Co., Phillipsburg, NJ). The plate was developed 10 cm in a tank saturated with ethylacetate:methanol:diethylamine (80:10:10).

Second 10-mL aliquots of blood and gastric samples were made alkaline with 0.5 mL of concentrated ammonium hydroxide and shaken with 10 mL of chloroform. The chloroform

was evaporated and the residue spotted twice on a silica gel plate then developed 10 cm in a tank saturated with methanol:ammonium hydroxide (98.5:1.5).

One acid plate was visualized with 0.1% diphenylcarbazone in 1% ethanolic mercuric chloride then heated at about 100°C under a heat lamp for 5 min [8]. The second plate was dipped in fresh 0.1% Fast Blue B (diazotized) dissolved in 50% ethanol:water [9]. One alkaline extract plate was visualized with iodoplatinate reagent [9]. The second plate was dipped in Marquis reagent then overstained in Forrest reagent [9].

Gas-Liquid Chromatography

Trimipramine, *N*-desmethyltrimipramine, and lidocaine were quantified by gas chromatography (GC) after the method of Foerster et al [10]. Clomipramine was used as the internal standard. Stock drug solutions at 100 μg/mL as the free bases were each prepared with 10% methanol in 0.1*N* hydrochloric acid. A drug-free blood was spiked with the above stock solutions to give 2000 ng/mL each of trimipramine and *N*-desmethyltrimipramine and 5.0 μg/mL of lidocaine. To 5.0 mL of whole blood (standard and case) were added 200 μL of clomipramine (100 μg/mL), 8 mL of 1-chlorobutane, and 1 mL of chloroform. The tube was mixed by inversion for 5 min, then eight drops of concentrated ammonium hydroxide were added and the tube mixed for a further 5 min. After a brief centrifugation, the organic phase was transferred to a clean tube, back-extracted into 4.0 mL of 1*N* hydrochloric acid by vortexing 1 min and then briefly centrifuged again. The hydrochloric acid layer was transferred to a 10-mL conical tube, aerated with nitrogen for 1 min, made basic with 1 mL of concentrated ammonium hydroxide, then extracted forward by vortexing into 1 mL of chloroform. After centrifugation, the aqueous phase was aspirated to waste. The chloroform was reduced in volume to about 30 μL, of which 3 μL were injected onto the gas chromatograph.

A Sigma 3 gas chromatograph fitted with a flame ionization detector, a model 023 chart recorder (all from Perkin Elmer, Norwalk, CT), and a model 3390A reporting integrator (Hewlett Packard, Palo Alto, CA) were used. Chromatography was effected on a 1.8-m by 2-mm inner diameter glass column packed with 3% SP2100 on 100–120 mesh Supelcoport (Supelco Inc., Bellefonte, PA). Nitrogen carrier gas flow was 25 mL/min, hydrogen was 30 mL/min, and air was 350 mL/min. The injector and detector tempeatures were 300°C. The oven was programmed after no initial delay from 170 to 275°C at 8C°/min with a 5-min final hold. Detector response was attenuated ×128. The reporting integrator used peak areas to calculate drug concentrations.

Blood alcohol determinations followed the method of Anthony et al [11] but with direct injection [12].

Gas Chromatography—Mass Spectrometry

A Finnigan Model 1020 mass-spectrometer (Finnigan MAT, Sunnyvale, CA) was used to confirm the identity of trimipramine, *N*-desmethyltrimipramine, lidocaine, and monoethylglycinexylidide. A 30-m by 0.25-mm inner diameter fused silica capillary column coated with 0.25-μm SE 30 (J and W Scientific) was used. Helium was used as a carrier gas at about 2 mL/min. Three microlitres of the extract were injected in the splitless mode; the injector was purged after 60 s. The remaining GC conditions were essentially the same as for the packed column.

Electron-impact ionization and a scan from 40 to 450 AMU each second was employed.

High Performance Liquid Chromatography

Phenobarbital and phenytoin were measured by high performance liquid chromatography (HPLC) at ambient temperature according to the method of Soldin [13].

Zomepirac was quantified by reverse phase HPLC using a method similar to that of Welch et al [*14*] except that the same mobile phase as above [*13*] was used at a flow rate of 0.8 mL/min. Under these conditions, zomepirac elutes at 2.9 min.

Results

Two drugs were visualized by TLC in the basic fraction of the blood extract at $R_f = 0.58$ and 0.35. The gastric extract showed only one drug at 0.56. These drugs stained positively with iodoplatinate and Forrest reagents. Authentic standards of trimipramine and *N*-desmethyltrimipramine migrated and stained in the same way. Other Forrest positive tricyclic antidepressants, namely imipramine, desipramine, clomipramine, and *N*-desmethylclomipramine behave distinctively different with $R_f = 0.43$, 0.22, 0.50 and 0.30, respectively.

The GC of the case blood specimen is shown in Fig. 1. Retention times for trimipramine/imipramine and *N*-desmethyltrimipramine/desipramine pairs are nearly identical. The mass spectra (Figs. 2 and 3) clearly identified only trimipramine and *N*-desmethyltrimipramine in the case blood extract. Lidocaine and its primary metabolite monoethylglycinexylidide were also confirmed from their mass spectra.

Phenobarbital and phenytoin were found to be present at subtherapeutic concentrations while zomepirac (therapeutic 0.5 to 1.5 μg/mL) and salicylates (therapeutic 20 to 200 μg/mL) were at lower therapeutic concentrations.

A summary of the results appears in Table 1.

Discussion

The blood concentration of trimipramine in this case is comparable with those of unpublished fatality reports held by the manufacturer.[4] In these reports, trimipramine blood concentrations ranged from 300 to 18 000 ng/mL. Unfortunately, most of these cases also involved other medications (for example, doxepin, chlordiazepoxide, perphenazine,

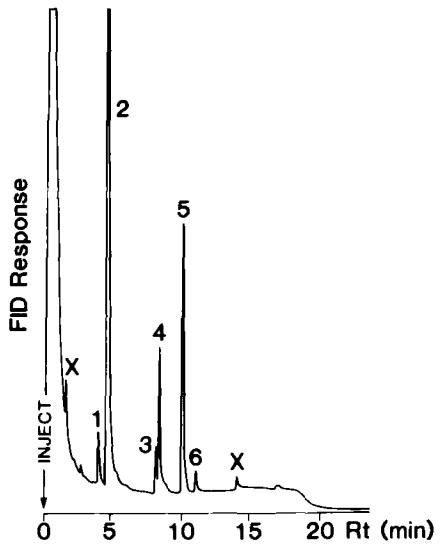

FIG. 1—*Gas chromatogram of case blood extract where Peak 1 is monoethylglycinexylidide, Peak 2 is lidocaine (6.7 μg/mL), Peak 3 is trimipramine (400 ng/mL), Peak 4 is* N*-desmethyltrimipramine (1130 ng/mL), Peak 5 is clomipramine (Internal Standard), Peak 6 is dioctylphthalate (contaminant), and* X *is unknown.*

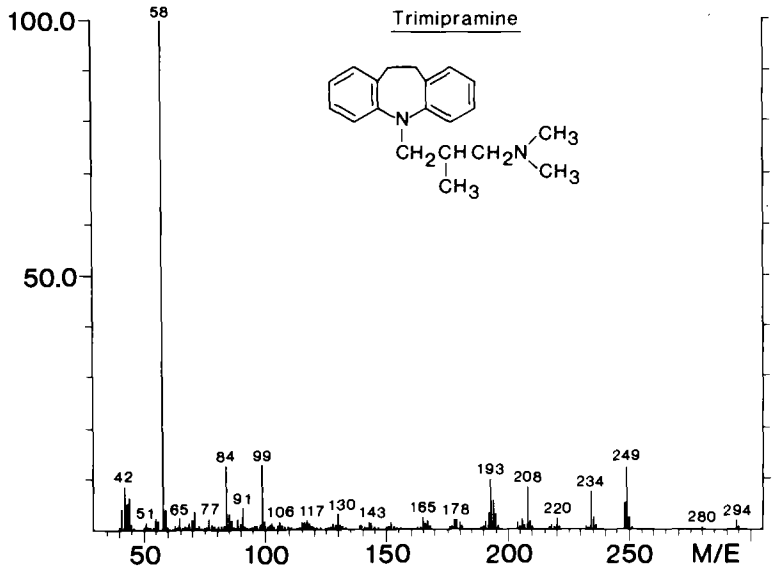

FIG. 2—*Mass spectrum of trimipramine.*

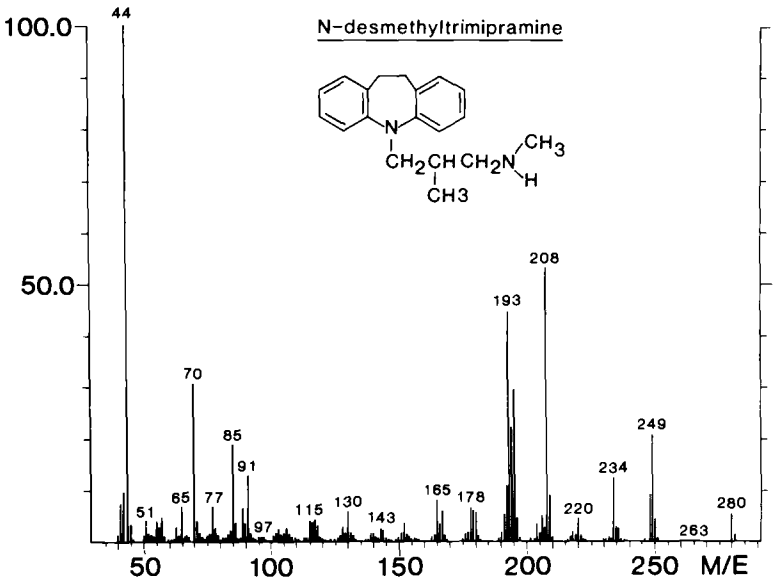

FIG. 3—*Mass spectrum of* N-*desmethyltrimipramine.*

methyprylon, flurazepam, and alcohol) and in no report was *N*-desmethyltrimipramine measured.

Pharmacologic information on trimipramine and its metabolite(s) is scanty. Therapeutic and toxic concentrations in plasma or whole blood have not been determined. Knowledge of the ratio of trimipramine to *N*-desmethyltrimipramine at steady state would help here to differentiate chronic from acute toxicity.

Principal toxicities of tricyclic antidepressants involve the nervous system and the heart.

TABLE 1—*Summary of toxicological findings.*

Gastric fluid: Trimipramine Positive	
Blood	
Trimipramine, ng/mL	400
N-desmethyltrimipramine, ng/mL	1130
Total, ng/mL	1530
Zomepirac, μg/mL	1.0
Lidocaine, μg/mL	6.7
Phenytoin, μg/mL	3.0
Phenobarbital, μg/mL	6.0
Salicylates, μg/mL	62
Alcohol, mg/100 mL	<5

Fatalities are common and severe cases of poisoning can result in profound coma; respiratory arrest; hypotension; status epilepticus; and any or all cardiac arrhythmias especially increasing intracardiac blocks, ventricular arrythmias, profound bradycardia, and asystole [*15,16*]. The deceased discussed above exhibited most of these signs. In addition, there was some evidence noted at autopsy of a preexisting cardiac abnormality, a predisposing factor for sudden death with tricyclic antidepressants [*16*].

The sum of the blood trimipramine and *N*-desmethyltrimipramine concentrations was 1530 ng/mL. Cardiac and respiratory toxicity leading to death has been associated with combined blood concentrations >1000 ng/mL for the more common tricyclic antidepressants [*17*]. This result is also consistent with fatality summaries of the other tricyclic antidepressants [*18-20*].

The recommended treatment protocol for tricyclic antidepressant overdosage [*16*] was not instituted; toxicological analyses of biological fluids were not performed before death.

The contribution of the elevated blood concentration of lidocaine (6.7 μg/mL; therapeutic 1.5 to 5.0 μg/mL) could not be ascertained. However, based on the moribund state of the patient upon arrival at hospital, it was not considered to be a significant factor. Also, the contribution of pimozide to death through potentiation of trimipramine could be ascertained. Pimozide in therapy and overdosage has not resulted in significant electrocardiographic, blood pressure, and pulse rate changes in animals and humans [*21*]. In support of a negligible contribution of pimozide to this death was its absence in any of the analytical workup.

It appears certain that a direct toxic action of trimipramine and *N*-desmethyltrimipramine on the heart or brain was responsible for this death. It has been suggested that in patients with genetically slow rates of metabolism of tricyclic antidepressants, the parent or active metabolites or both may accumulate gradually in the brain and heart tissue until they exceed a toxic threshold resulting in convulsions, cardiac arrhythmias, and death [*22*].

Acknowledgment

We would like to thank Dr. R. Fontaine and Mr. M. Golden of Rhône-Poulenc Pharma Inc., Montreal, Quebec for providing pure powders of trimipramine maleate and *N*-desmethyltrimipramine mealeate and for their unpublished trimipramine fatality reports. The secretarial skills of Miss M. A. Beck are appreciated.

References

[*1*] Settle, E. C., Jr. and Ayd, F. J., Jr., "Trimipramine: Twenty Years Worldwide Clinical Experience," *Journal of Clinical Psychiatry*, Vol. 41, No. 8, Aug. 1980, pp. 266-274.

[2] Berstad, A., Bjerke, K., Carlsen, E., and Aadland, E., "Treatment of Duodenal Ulcer with Antacids in Combination with Trimipramine or Cimetidine," *Scandanavian Journal of Gastroenterology*, Vol. 15 (Supplement 58), 1980, pp. 46-52.

[3] Bohman, T., Myren, J., Flaten, O., and Schrumpf, E., "The Effect of Trimipramine, Cimetidine and Atropine on Gastric Secretion," *Scandanavian Journal of Gastroenterology*, Vol. 15 (Supplement 58), 1980, pp. 53-56.

[4] Siurala, M., "The Possible Significance of the Central Action of Trimipramine in the Treatment of Functional 'Non-Ulcer' Dyspepsia and Peptic Ulcer with Masked Depression," *Scandanavian Journal of Gastroenterology*, Vol. 15 (Supplement 58), 1980, pp. 57-58.

[5] Valnes, K., Wetterhus, S., Ellekjaer, E., Halvorsen, L., Hovdenak, N., Larsen, S., Skaug, O. E., Tonder, M., and Myren, J., "Trimipramine in the Treatment of Duodenal Ulcer. A Multicenter, Open Study," *Scandanavian Journal of Gastroenterology*, Vol. 15 (Supplement 58), 1980, pp. 65-70.

[6] Valnes, K., Skaug, O. E., Larsen, S., and Myren, J., "Trimipramine and Duoedenal Ulcer," *Scandanavian Journal of Gastroenterology*, Vol. 15 (Supplement 58), 1980, pp. 71-78.

[7] Daneshmend, T. K., Homeida, M. M. A., Mountford, R. A., Brown, P., and Neumann, C. S., "Clinical Trial Value of Trimipramine Versus Placebo in Duodenal Ulcer Healing," *Gut*, Vol. 22, No. 12, Dec. 1981, pp. 1045-1047.

[8] Smith, I. and Seakins, J. W. T., Eds., *Chromatographic and Electrophoretic Techniques*, Vol. 1, 4th ed., William Heinemann Medical Books Ltd., London, Great Britain, 1976, p. 412.

[9] Clark, E. C. G., Ed., *Isolation and Identification of Drugs*, Vol. II, Pharmaceutical Press, London, Great Britain, 1975, p. 1175.

[10] Foerster, E. H., Hatchett, D., and Garriott, J. C., "A Rapid Comprehensive Screening Procedure for Basic Drugs in Blood or Tissues by Gas Chromatography," *Journal of Analytical Toxicology*, Vol. 2, No. 2, March/April 1978, pp. 50-55.

[11] Anthony, R. M., Sutheimer, C. A., and Sunshine, I., "Acetaldehyde, Methanol and Ethanol Analysis by Headspace Gas Chromatography," *Journal of Analytical Toxicology*, Vol. 4, No. 1, Jan./Feb. 1980, pp. 43-45.

[12] Jain, N. C., "Direct Blood Injection Method for Gas Chromatographic Determination of Alcohols and Other Volatile Compounds," *Clinical Chemistry*, Vol. 17, No. 2, Feb. 1971, pp. 82-85.

[13] Soldin, S. J. and Hill, J. G., "Rapid Micromethod for Measuring Anticonvulsant Drugs in Serum by High-Performance Liquid Chromatography," *Clinical Chemistry*, Vol. 22, No. 6, June 1976, pp. 856-859.

[14] Welch, C. L., Annesley, T. M., Luthra, H. S., and Moyer, T. P., "Liquid Chromatographic Determination of Zomepirac in Serum and Plasma," *Clinical Chemistry*, Vol. 28, No. 3, March 1982, pp. 481-484.

[15] Rose, J. B., "Tricyclic Antidepressant Toxicity," *Clinical Toxicology*, Vol. 11, No. 4, Nov. 1977, pp. 391-402.

[16] Crome, P., "Antidepressant Overdosage," *Drugs*, Vol. 23, No. 6, June 1982, pp. 431-461.

[17] Petit, J. M., Spiker, D. G., Ruwitch, J. F., Ziegler, V. E., Weiss, A. N., and Biggs, J. T., "Tricyclic Antidepressant Plasma Levels and Adverse Effects After Overdose," *Clinical Pharmacology and Therapeutics*, Vol. 21, No. 1, Jan. 1977, pp. 47-51.

[18] Bailey, D. N. and Shaw, R. F., "Tricyclic Antidepressants: Interpretation of Blood and Tissue Levels in Fatal Overdose," *Journal of Analytical Toxicology*, Vol. 3, No. 2, March/April 1979, pp. 43-46.

[19] Robinson, A. E., McDowall, R. C., Sattar, H., Holder, A. T., and Powell, R., "Tricyclic and Tetracyclic Antidepressant Drugs: Forensic Toxicology of Some Autopsy Cases," *Journal of Analytical Toxicology*, Vol. 3, No. 1, Jan./Feb. 1979, pp. 3-13.

[20] Haggani, M. T. and Gutteridge, D. R., "Two Cases of Clomipramine Hydrochloride (Anafranil) Poisoning," *Forensic Science International*, Vol. 3, No. 1, Jan./Feb. 1974, pp. 83-87.

[21] Pinder, R. M., Brogden, R. N., Sawyer, P. R., Speight, T. M., Spencer, R., and Avery, G. S., "Pimozide: A Review of its Pharmacological Properties and Therapeutic Uses in Psychiatry," *Drugs*, Vol. 12, No. 1, July 1976, pp. 1-40.

[22] Singh, G., "Cardiac Arrest with Clomipramine," *British Medical Journal*, Vol. 3, No. 5828, 16 Sept. 1972, p. 698.

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