CASE REPORT

L. R. Bednarczyk,[1] *Ph.D.; C. V. Wetli,*[2] *M.D.; and Joseph Balkon,*[3] *Ph.D.*

Respirator Toxicology

REFERENCE: Bednarczyk, L. R., Wetli, C. V., and Balkon, J., **"Respirator Toxicology,"** *Journal of Forensic Sciences*, JFSCA, Vol. 26, No. 2, April 1981, pp. 373-380.

ABSTRACT: A case of delayed death resulting from drowning was investigated. A disparity in the propoxyphene concentrations determined in antemortem and postmortem specimens appeared to exist. The disparity is apparently a product of the fact that cardiopulmonary function had been maintained artificially for 57 h, with subsequent tissue autolysis that was demonstrated microscopically. Interpretation of laboratory findings on postmortem specimens must be done with caution when the interval between drug exposure and death has been interrupted by respirator therapy.

KEYWORDS: toxicology, pathology and biology, respirators, propoxyphene

Advanced techniques of cardiopulmonary resuscitation and the rapid deployment of skilled paramedical rescue teams have saved countless lives of victims of trauma and natural disease alike. However, clinical and pathological artifacts may result when rescue units encounter a victim who is at or near brain death. When this condition occurs, cardiopulmonary function may subsequently be artificially maintained by a variety of life support systems. Such states of simulated life may have varying degrees of organ autolysis superimposed on the initiating disease or injury. Such artifacts create interpretive problems for both the forensic pathologist and the forensic toxicologist. The case reported here describes an apparently inordinately elevated postmortem blood propoxyphene concentration in a woman whose life support systems were discontinued 57 h after her drowning incident. The official cause of death was listed as drowning, with the toxicology findings as a contributory factor.

Case Report

A 32-year-old white woman was found at the bottom of a public swimming pool. Although the time of submersion was not known, witnesses estimated an elapsed time of 3 to 4 min. The victim was retrieved from the pool and cardiopulmonary resuscitation was administered

Received for publication 12 May 1980; revised manuscript received 22 Sept. 1980; accepted for publication 25 Sept. 1980.

[1]Director of laboratories, Medical Examiner's Office, Dade County, Fla., and clinical assistant professor of pathology, University of Miami School of Medicine, Miami, Fla.

[2]Associate medical examiner, Dade County, Fla., and assistant professor of pathology, University of Miami School of Medicine, Miami, Fla.

[3]Chief toxicologist, Long Island Jewish-Hillside Medical Center, Glen Oaks, N.Y.

by a physician who was at the scene. She was cyanotic and unconscious, had dilated pupils, and was without any vital signs upon the arrival of a fire rescue unit 2 min later. Sodium bicarbonate, calcium chloride, epinephrine, and dextrose in water were all administered intravenously at the scene. While en route to a local hospital, the victim regained a normal sinus heart rhythm of 80/min, which subsequently increased to 100/min. Upon her arrival in the hospital emergency room spontaneous respirations commenced. Her pupils, however, remained fixed and dilated, and she was areflexic. Neurological examination failed to elicit any evidence of cerebral function above the respiratory level in the lower medulla. Following a transient slight improvement in her neurological status, she developed pulmonary edema, myoclonic seizures, and acute renal failure. Hospital treatment consisted of the administration of corticosteroids, the administration of amobarbital to control seizures, and hemodialysis followed by peritoneal dialysis. The results of liver function tests performed on the day of her death were as follows: total bilirubin, 2.7 mg/dL (normal, 0.2 to 1.2 mg/dL); serum glutamic oxalacetic transaminase, greater than 4500 units/L (normal, 0 to 41 units/L); lactic dehydrogenase, 4725 units/L (normal, 60 to 100 units/L). The creatine phosphokinase concentration, measured at the same time, was 2889 units/L (normal, 0 to 225 units/L). About 57 h after admission she was found in cardiac asystole with pupils fixed at 2.0 mm and without spontaneous respiration. She was pronounced dead at that time.

Pathology

Postmortem examination revealed anasarca, 1 L of clear fluid in the peritoneal cavity, and 700 mL of serosanguineous fluid in each pleural space. Icterus was not evident. Scattered small accumulations of blood were found in the retroperitoneal space, and the lesser omental sac had a 300-mL hematoma. The heart was normal. The lungs had a combined weight of 1675 g. They were airless, markedly congested, and edematous. Cut surfaces of the 1950-g liver were mottled yellow and brown. The pale kidneys had cut surfaces that were glassy and bulged above the plane of sectioning. The 1310-g brain was edematous and congested. Microscopic examination revealed massive autolysis. In the liver this was predominantly centrilobular with relative preservation of hepatocytes in periportal areas (Fig. 1). Additionally, cholangiectasis with bile stasis was prominent. The brain revealed changes typical of simulated life ("respirator brain," Fig. 2).

Toxicology

Sample Preparation

The blood samples analyzed were diluted 1:1 with deionized water. The liver tissue was homogenized with deionized water at a ratio of one part tissue to three parts water.

Extraction of Propoxyphene and Metabolites

The isolation of propoxyphene was accomplished by using the procedure outlined in Fig. 3. Three millilitres of the blood or tissue homogenate and the appropriate controls and standards were mixed with 100 μL of the internal standard solution (100 μg/mL propyladiphenine [SKF 525-A] in absolute methanol).

Following the addition of 0.5 mL of pH 9.5 carbonate buffer (0.1*M*), the compounds of interest were extracted by mixing this aqueous biological mixture in a vortex with 10 mL of hexane/isoamyl alcohol (85:15) extraction solvent. The aqueous phase was then discarded and the organic phase was extracted initially with 1.2 mL of 0.1*N* hydrochloric acid and then with 0.5 mL of 6*N* hydrochloric acid.

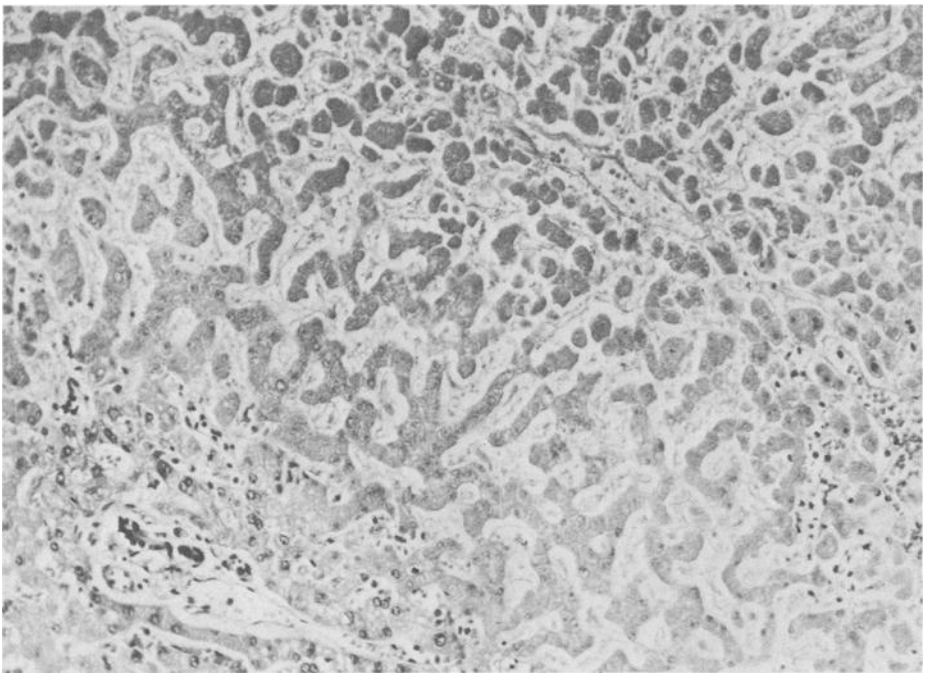

FIG. 1—*Photomicrograph of liver showing massive autolysis.*

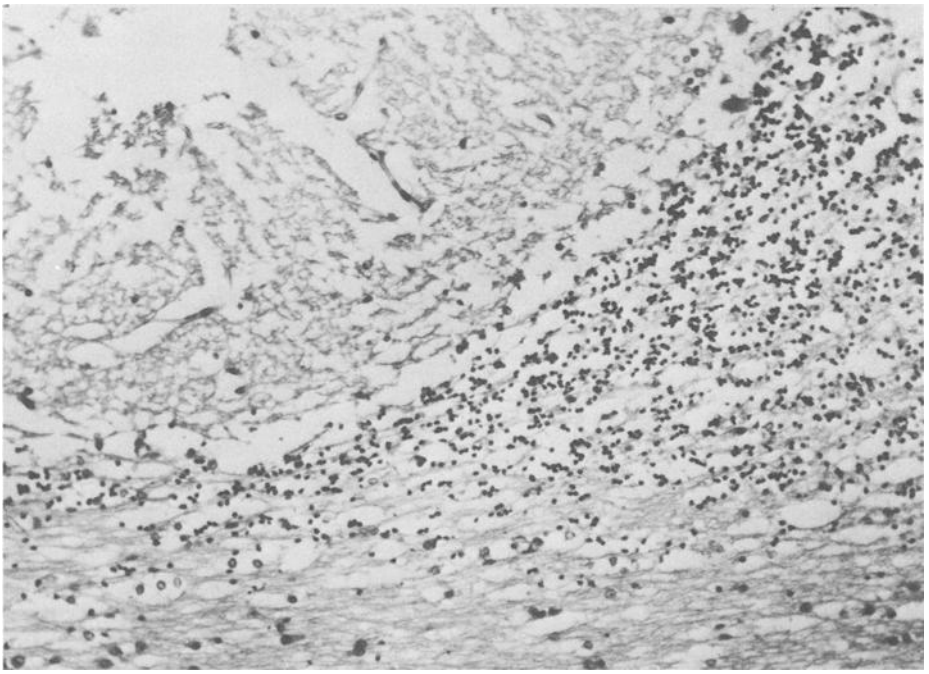

FIG. 2—*Photomicrograph of cerebellum showing change typical of "respirator brain."*

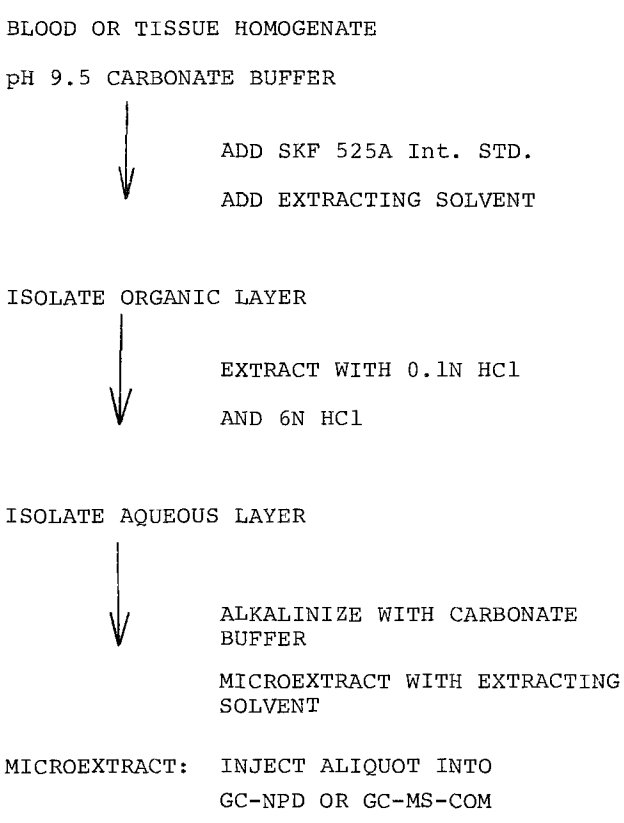

FIG. 3—*Outline of isolation procedure used to detect propoxyphene.*

The organic phase was then discarded and the remaining aqueous phase was made alkaline by adding the pH 9.5 carbonate buffer.

The final extract was prepared by adding 50 μL of toluene/isoamyl alcohol (85:15) extracting solvent to the alkaline aqueous layer in a 5-mL conical centrifuge tube. After the mixing in the vortex and centrifugation, aliquots of the toluene/isoamyl alcohol organic layer were injected into either a Perkin-Elmer Model 900 gas chromatograph equipped with a nitrogen-phosphorus detector or a Hewlett-Packard 5982A gas chromatograph-mass spectrometer-computer system. Details of this isolation approach, particularly for tissue analysis, are currently in preparation for publication.

Chromatographic Conditions

Chromatography of these extracts was accomplished on a 1.8-m (6-ft) glass column packed with 3% OV-17 on Chromosorb W, with helium as a carrier gas. The column oven during an analytical run was programmed from 190 to 265°C at 6°C/min. The injection port and manifold temperatures were each maintained at 250°C.

The chromatographic effluents were passed directly to a Perkin-Elmer nitrogen-phosphorus detector, optimized for detectability in the nitrogen mode.

Alternatively, chromatography was accomplished in the Hewlett-Packard 5982 system on a 0.9-m (3-ft) glass column packed with 1% OV-17. The oven temperature was programmed

from 150 to 260°C at 8°C/min. Chromatographic effluents were transferred to the ion source of the mass spectrometer via a membrane separator. These conditions allowed reproduction of the retention times observed in the Perkin-Elmer system.

The mass spectrometer was operated in electron impact mode, with a mass scan range of 50 to 400 AMU. Other operating conditions were standard, as specified by the 5933 computer requirements. After the acquisition of analytical data, the stored information was processed according to a selected ion profile analysis.

Results

The nitrogen-phosphorus detector gas chromatographic tracings obtained are shown in Fig. 4. These tracings indicate the positive finding for propoxyphene as well as its metabolic products in all the specimens analyzed.

The gas chromatographic/mass spectrometric/computer analysis by selected ion profiles of these same extracts indicated that propoxyphene and certain metabolites were indeed present (Fig. 5). Also identified with a selected ion profile technique was diazepam. Following the calibration of each system for propoxyphene, norpropoxyphene, and diazepam, the concentrations of these substances in the specimens submitted were determined (Table 1).

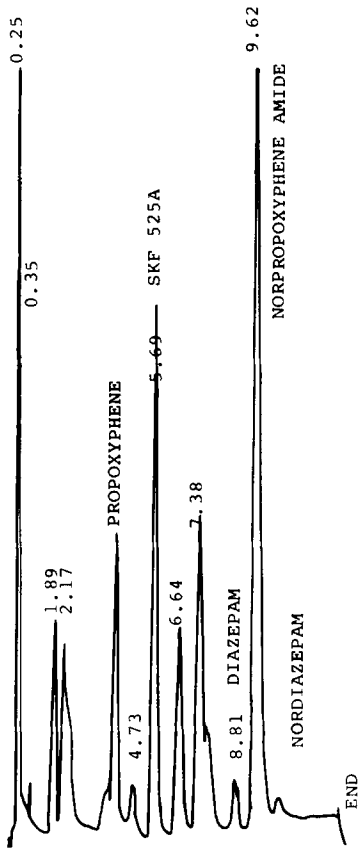

FIG. 4—*Gas chromatogram (nitrogen-phosphorus detector) of liver extract.*

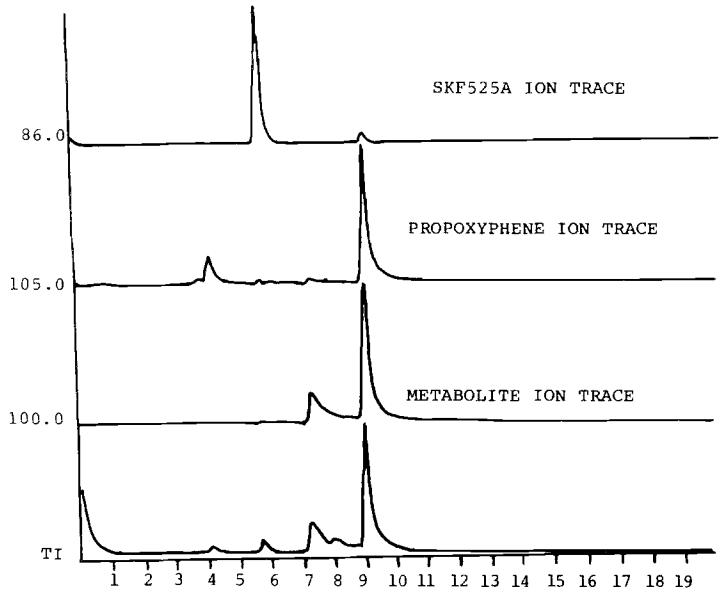

FIG. 5—*Gas chromatographic/mass spectrometric/computer traces of liver extract. Ion traces for screening purposes included* m/e *86, internal standard;* m/e *105, propoxyphene's major fragment;* m/e *100, metabolite's major fragment; and* TI, *total ion chromatogram.*

TABLE 1—*Drug concentrations found, in mg/L.*

Specimen	Propoxyphene	Norpropoxyphene	Diazepam
Premortem blood	0.42	1.9	0.41
Postmortem blood	1.1	7.7	0.95
Liver	2.8	37.0	0.51

Discussion

Propoxyphene is metabolized primarily by *N*-demethylation in the liver to norpropoxyphene [*1*]. Administration of therapeutic amounts results in peak blood concentrations of 0.2 to 0.3 mg/L for both propoxyphene and norpropoxyphene [*1,2*]. Chronic oral administration of the drug results in blood concentrations of 0.10 to 0.42 mg/L propoxyphene and 0.8 to 1.45 mg/L for norpropoxyphene [*1,3*]. The plasma half-life of propoxyphene and norpropoxyphene are said to be 12 and 36 h, respectively [*2,3*]. Propoxyphene concentrations of 1 mg/L or more in blood are indicative of serious toxicity, and levels of 2 mg/L or more are consistent with a fatal exposure [*1*]. Liver concentrations of the parent drug and its major metabolite can exceed blood concentrations by a factor of 10 or more in an acute overdose, whereas they more nearly approach the blood concentrations with chronic usage [*1,4*]. Norpropoxyphene is said to have one fourth to one half the analgesic activity of propoxyphene [*1*]. Although it does not cross the blood-brain barrier as readily as propoxyphene [*4*], its role in toxicity cannot be ignored [*1,2*].

In the case described, the premortem concentrations of propoxyphene and norpropoxy-

phene in the blood reflect a toxic state. The ratio of propoxyphene to norpropoxyphene indicates chronic usage. Analysis of the blood taken at autopsy revealed a fivefold increase in propoxyphene and an approximately eightfold increase in norpropoxyphene over the premortem concentrations despite the fact that no propoxyphene was administered to the victim after the drowning incident.

Two possible explanations for this apparent inconsistency are likely. First, the victim consumed a large amount of propoxyphene just prior to the incident, drowned, and continued to absorb the drug while hospitalized. Second, the induced state of simulated life, with its attendant organ autolysis, liberated large amounts of stored drug into the systemic circulation. Against the first hypothesis are these factors:

1. The ratio of propoxyphene to norpropoxyphene of 1:4.5 in the premortem blood is consistent with chronic propoxyphene use.
2. Investigation revealed the victim was a chronic propoxyphene abuser.
3. Witnesses to her activities prior to the incident tend to rule out a suicidal or accidental ingestion of medication.
4. Emergency room records indicate that a lavage was performed upon admission, but the specimen was never submitted for analysis.

The most compelling facts to refute Hypothesis 1 and to support Hypothesis 2 are that since the half-life of propoxyphene averages 8 h, the compound is rapidly absorbed from the gastrointestinal tract, and peak blood concentrations occur in about 2 h, the blood concentration after 57 h would be extremely low or nonexistent, not increased threefold.

Laboratory data of liver function on the day the patient died reflected massive acute hepatic failure, which was probably initiated by the drowning incident and not ameliorated by the hospitalization. This event was subsequently confirmed morphologically (Fig. 1).

The underlying effect is the dissolution of hepatocellular membranes, which releases the contents of the cells into the general circulation. Hence, the elevated levels of enzymes such as serum glutamic oxalacetic transaminase and stored substances such as bilirubin reflect the degree of loss of hepatic integrity. Loss of the integrity of the hepatocellular membrane most likely accounts for stored propoxyphene's and norpropoxyphene's being dumped into systemic circulation.

In this case, and taken by themselves, the concentrations of propoxyphene and norpropoxyphene would suggest an acute overdose. Proper interpretation of the postmortem data appears to depend on the antemortem levels.

The case serves to illustrate a potential pitfall in the interpretation of toxicologic results when cardiopulmonary function has been maintained artifically and when the inevitable organ autolysis results. The data presented indicate that every effort should be made to obtain antemortem specimens.

As the pathologist has learned to recognize artifacts associated with brain death, so too must the toxicologist become aware of seemingly spurious and bizarre results induced by artificially prolonged cardiopulmonary function.

References

[1] Baselt, R. C., *Disposition of Toxic Drugs and Chemicals in Man*, Vol. 1, Biomedical Publications, Canton, Conn., 1978, pp. 34–37.

[2] Finkle, B. S., McCloskey, K. L., Kiplinger, G. F., and Bennett, I. F., "A National Assessment of Propoxyphene in Postmortem Medicolegal Investigation, 1972–1975," *Journal of Forensic Sciences*, Vol. 21, No. 4, Oct. 1976, pp. 706–742.

[3] McBay, A. J., "Propoxyphene and Norpropoxyphene Concentrations in Blood and Tissues in Cases of Fatal Overdose," *Clinical Chemistry*, Vol. 22, No. 8, Aug 1976, pp. 1319–1321.

[4] Baselt, R. C., Wright, J. A., Turner, J. E., and Cravey, R. H., "Propoxyphene and Norpropoxy-

phene Tissue Concentrations in Fatalities Associated with Propoxyphene Hydrochloride and Propoxyphene Napsylate," *Archives of Toxicology*, Vol. 34, 1975, pp. 145-152.
[5] Goodman, L. S. and Gilman, A., *The Pharmacological Basis of Therapeutics*, 5th ed., McMillan, New York, 1975, pp. 270-271.

Address requests for reprints or additional information to
Leonard R. Bednarczyk, Ph.D.
Medical Examiner's Office
1050 N.W. 19th St.
Miami, Fla. 33136