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Incidence of Propoxyphene Poisoning: A Report of Fatal Cases

Propoxyphene hydrochloride, since its introduction in late 1957, has become a widely prescribed drug because of its presumed efficacy as an equivalent to narcotics and its low incidence of side effects. Miller [*1*], based on his critical review of the drug, found that dextropropoxyphene is ironically "no more effective than aspirin or codeine and may even be inferior to those analgesics" although more prescriptions for dextropropoxyphene were dispensed in this country in 1969 than for any other drug.

Bogartz and Miller [*2*] reported in 1971 that their search of the literature had uncovered only 19 cases of serious intoxication, and recently Young [*3*] reported nine cases of suicide due to ingestion of propoxyphene and noted that only five deaths had been previously reported. Worm [*4*] reported nine cases of poisoning in a one-year period which were attributed to dextropropoxyphene as the sole or contributory cause of death. Tennant [*5*] states that 21 deaths due to the administration of drugs have occurred among U.S. Army personnel in Europe since 1968. Thirteen of these deaths were attributed to propoxyphene hydrochloride overdose.

The authors of this study are beginning to see an increase in the abuse potential and the danger of this drug. This report is intended to present data for suicides, accidental deaths, and selected multiple drug deaths where propoxyphene has caused death or contributed to the terminal episode. This study, covering a five-year period, is taken from coroners' cases from three California counties with a total population of more than ten million people. Propoxyphene was involved in 238 fatal cases during this period.

Methods of Analysis

Inasmuch as three laboratories were involved in this study and the time period was of long duration, multiple methods were used in the isolation, identification, and estimation of drug levels from the biological samples.

Propoxyphene was isolated from body fluids and tissues by extracting at alkaline pH into organic solvents such as diethyl ether and chloroform. Another solvent used successfully by Wolen et al [*6*] was butyl chloride. This had been used by Wolen et al to extract plasma over a wide pH range of 6.1 to 11.3. Finkle [*7*] extended the use of butyl chloride to the extraction of tissue homogenates as well as blood and plasma.

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Once isolated, screening for propoxyphene was accomplished by thin-layer chromatography [*8*, *9*, *10*].

One of the earlier techniques involved the use of paper and thin-layer chromatography for isolation of the compound. The spot was then cut out or scraped off, transferred to a test tube, and subjected to the methyl orange colorimetric method of Brodie et al [*11*]. This modification of Brodie's technique provided a degree of specificity to the method. Also among the methods used was that of Wallace et al [*12*], which involves refluxing the extracted propoxyphene to form a "reaction product." The product formed is steam distilled and has spectrophotometric sensitivity in the ultraviolet range of approximately 50 times that of the parent compound. In a more recent report, Wallace et al [*13*] utilized a combination of ultraviolet spectrophotometric and gas chromatographic techniques which provided a specific quantitative method for determining the drug in biological extracts. Another chemical method used was that of Thompson et al [*14*] which involves the exposure of the extracted drug to ultraviolet radiation for 45 min. The ultraviolet spectrum is recorded using the unexposed solution as a reference. The radiation produces a marked increase in absorption at 253 mμ and provides both sensitivity and specificity. Methadone, however, does interfere and must be separated before quantitation of propoxyphene is made. The method is best used when the drug concentration is 10 μg/g or more. McBay et al [*15*] recently reported that most of the propoxyphene in liver and urine is conjugated and that acid hydrolysis not only liberates the conjugated form but also causes the formation of a new compound which has an ultraviolet absorbance far greater than the parent compound. In their method, as in Thompson et al [*14*], ultraviolet irradiation further increases the absorbance and enhances sensitivity.

In addition to thin-layer chromatography, one laboratory used infrared spectrophotometry to provide proof of identity. The drug, isolated by thin-layer chromatography, is scraped off the plate into a small tube where extraction is accomplished at approximately pH 9 with organic solvent. The solvent is isolated and evaporated to near dryness without heat or acid. The residue is then mixed with potassium bromide and a micro pellet is formed. Satisfactory infrared spectra have been obtained by this method.

All three reporting laboratories involved in this study have also used gas chromatography extensively for the qualitative and quantitative determination of propoxyphene. Several quite reliable gas chromatographic methods have been used [*6*, *7*, *13*, *16*]. One which has been modified and adapted to the routine quantitative identification of propoxyphene in our laboratories involves the use of lidocaine as an internal standard. To a 5-ml sample of blood (or a 1- to 2-g tissue homogenate) add 1 ml of 5 μg of lidocaine/ml of water, and buffer the solution to approximately pH 9 with solid sodium borate. Then extract the sample with 2 to 3 volumes of dichloromethane. Following centrifugation, remove the aqueous layer by aspiration and discard. The filtered solvent is then extracted twice with 1 volume of 0.5 *N* sulfuric acid. Then adjust the combined acid solutions to pH 9.0 with solid sodium borate and extract with 0.5 ml dichloromethane. Remove the solvent and evaporate under a stream of nitrogen in a 35°C water bath to about 10 μl. Inject 2 μl into a gas chromatograph, fitted with a flame ionization detector and a 2 ft (.6 m) long glass column, 4 mm in diameter, packed with 2.5 percent SE 30 on acid washed silanized Chromosorb Q, 80–100 mesh. The conditions for the gas chromatographic separation are an injector temperature of 205°C, a column temperature of 190°C, a detector temperature of 205°C, and a nitrogen flow rate of approximately 40 ml/min. Figure 1 shows a typical chromatogram of an extract from liver tissue. Recovery is 95 percent or better by this method. Propoxyphene and lidocaine peak high ratios are calculated for various ranges of concentration.

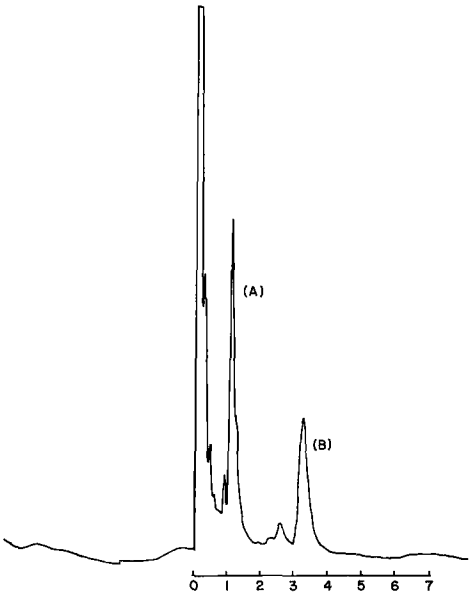

FIG. 1—*Separation of products from extracted liver tissue. (A) is lidocaine and (B) is propoxyphene.*

Although various methods were used in the three laboratories during the course of this study, each method was carefully evaluated for accuracy, sensitivity, and reproducibility. A series of propoxyphene standards were analyzed along with tissues from each case.

Distribution of Propoxyphene in the Tissue

Emmerson et al [*17*] reported peak blood propoxyphene levels in rats after oral dosage of 20 mg/kg at 120 min. Rats sacrificed at that time interval were found to have brain propoxyphene levels slightly lower than those found in the blood, but kidney levels were twice those of blood, and liver levels were 12 times those of blood levels. After introducing 10 mg/kg single doses of the *N*-methyl ^{14}C labeled drug intravenously into rats, the authors reported peak blood levels at 1 min and found concentrations of the drug in lung, heart, kidney, adrenal, and brain tissue that were 10–20 times greater than those in the blood.

In the body distribution studies published by Worm [*4*] from selected fatal human cases, brain propoxyphene levels were lower than those of the blood and the liver levels were significantly higher than both. In her analysis of blood, brain, liver, bile, and kidneys by gas chromatography, the highest levels were found in the liver and bile.

In our study, from fatal cases involving only propoxyphene, blood levels ranged from 0.1 mg/100 ml to 6.0 mg/100 ml (Fig. 2). Liver levels from fatal cases attributed to propoxyphene overdosage, and in which alcohol and other drugs were not found, ranged from 0.5 mg/100 g wet tissue to 55.0 mg/100 g wet tissue (Fig. 3).

Blood to liver ratios from 16 cases are given in Table 1. Alcohol was found in 65 cases in which the only other drug found was propoxyphene (Table 2). In more than 50 cases propoxyphene was found in combination with one or more drugs, excluding alcohol.

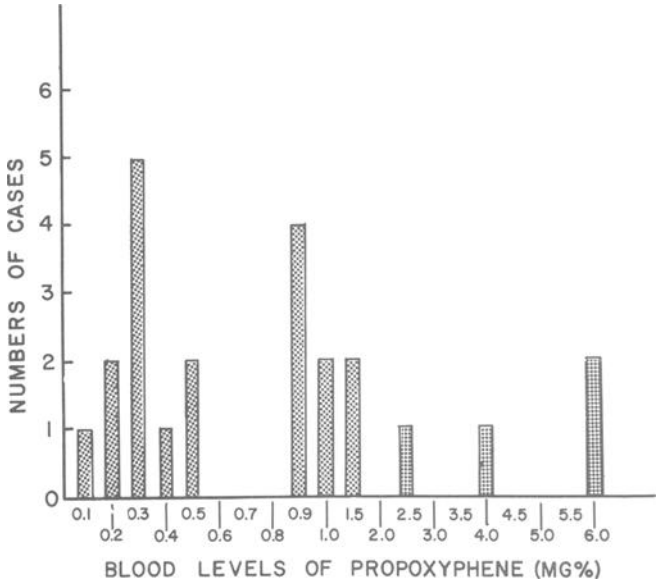

FIG. 2—*Range of propoxyphene blood concentrations from fatal cases.*

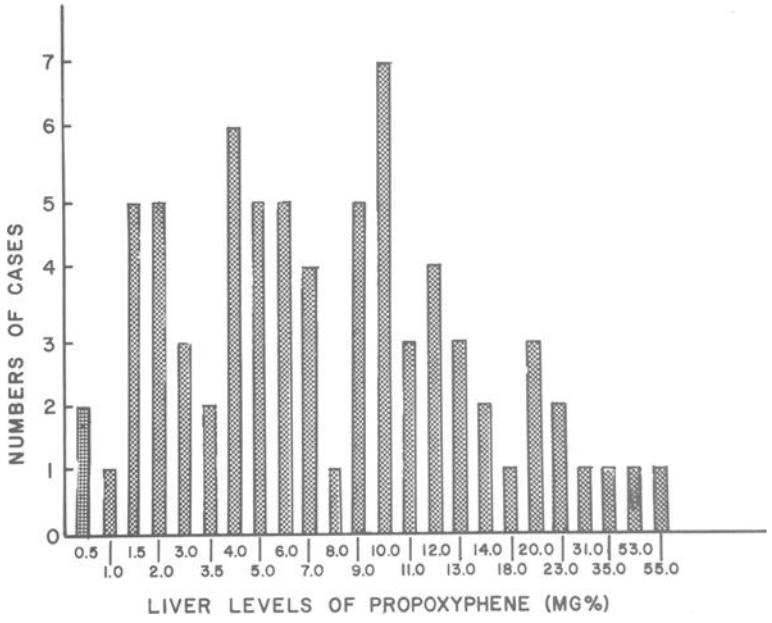

FIG. 3—*Range of propoxyphene liver concentrations from fatal cases.*

TABLE 1—*Blood and liver propoxyphene concentration from Coroner's cases.*

Age	Sex	Blood, mg/100 ml	Liver, mg/100 g	Total Stomach	Classification
29	F	0.95	8.9	Trace	Undetermined
19	M	0.9	12.6	4.4 mg	Undetermined
42	F	0.3	15.0	60.7 mg	Suicide
22	M	4.0	35.3	160 mg	Suicide
47	F	0.37	30.9	356 mg	Suicide
49	F	5.8	23.4	20 mg	Suicide
19	F	1.0	9.8	256 mg	Suicide
52	F	0.3	1.7	Trace	Undetermined
17	M	0.2	3.2	0.8 mg	Accidental
55	F	0.5	2.3	1.1 mg	Accidental
62	F	0.15	1.2	Trace	Accidental
2	M	0.3	3.9	42 mg	Accidental
55	M	0.3	15.1	170 mg	Suicide
52	F	0.3	1.7	12 mg	Accidental
62	F	0.2	1.2	240 mg	Accidental
43	F	0.9	22.2	n/a	Suicide

n/a = not available.

Analysis of propoxyphene by multiple methods has previously been described. These figures constitute findings from all three laboratories.

Report of Selected Cases

In nine of the cases analyzed by the three laboratories engaged in this study, case histories gave strong evidence of the total dosage ingested.

Case 1

A 20-year-old female and her roommate were lying on separate beds talking. The 20-year-old appeared to be drowsy. The roommate dozed off and was awakened some ten minutes later by the telephone. At that time she noted that the 20-year-old was cyanotic and not breathing. A prescription bottle found in the purse revealed that 50 Darvon® capsules had been issued the day before death. Twenty-eight capsules remained in the bottle.

Pathology—In the lungs parenchyma revealed mild congestion.

Toxicology—The propoxyphene levels are given in Table 3.

Case 2

A 47-year-old male was found dead in his apartment. The body was in hard rigor and cyanotic in all dependent portions. The investigation gave evidence that approximately 100 Darvon® capsules had been ingested.

Pathology—Visceral congestion.

Toxicology—Alcohol was found present in addition to propoxyphene. See Table 3.

Case 3

A 49-year-old male with a history of diabetes, chronic pulmonary disease, and alcoholism had been prescribed phenformin, Amesec®, nitroglycerin, and Darvon®. As a result of intense pain, he allegedly ingested more than 30 Darvon® capsules within a few

TABLE 2—*Blood alcohol and liver propoxyphene concentrations from 64 Coroner's cases in which only these drugs were found.*

Blood Alcohol Concentration, mg/100 ml	Liver Propoxyphene Concentration, mg/100 g	Number of Cases
20	5.3	1
30	3.7	1
60	1.8, 3.5, 8.1	3
80	1.2, 3.9, 7.3, 10.9	4
90	5.0, 5.1, 7.9, 11.3	4
100	0.6, 2.8	2
110	0.5, 3.6, 7.7	3
120	15.5, 26.4	2
130	4.4, 8.0, 11.8, 11.9	4
140	2.1, 11.8, 15.9	3
150	27.6	1
160	15.0	1
170	0.5, 1.7	2
180	0.8, 0.9, 24.4, 25.2	4
190	5.4	1
200	2.1, 2.6, 6.8, 6.8, 7.1, 36.2	6
210	2.3, 3.1, 8.3, 35.9, 38.4	5
230	1.9, 23.2	2
240	0.2	1
250	2.5, 2.8, 5.8, 6.7, 12.2, 12.4, 23.8	7
260	0.5, 1.2	2
270	10.9	1
280	2.2, 4.8	2
290	23.0	1
430	13.4	1

TABLE 3—*Toxicological data from selected fatal cases.*

Case	Age	Sex	Probable Amount Ingested	Dose	Blood, mg/100 ml	Liver, mg/100 g	Total Gastric	Other Drugs
1	20	F	1.4 g	15 mg/kg	n/a	12.0	12.9 mg	Short-acting barbiturate, blood 0.3 mg/100 ml
2	47	M	6.5 g	65 mg/kg	Trace	10.9	44 mg	Blood alcohol 80 mg/100 ml
3	49	M	1.9 g	15 mg/kg	0.56	5.3	n/a	
4	44	F	1.9 g	18 mg/kg	5.8	23.4	20 mg	
5	41	F	1.3 g	15 mg/kg	0.27	13.4	7.3 mg	Blood alcohol 430 mg/100 ml
6	17	M	1.6 g	20 mg/kg	1.5	5.6	20 mg	
7	36	F	3.2 g	61 mg/kg	1.8	9.8	158 mg	
8	55	M	3.4 g	45 mg/kg	0.3	4.0	170 mg	
9	43	M	4.5 g	41 mg/kg	2.3	34.1	8 mg	Phenobabital—blood 5.3/100 ml, liver 10.9/100 g

n/a = not available.

hours of hospitalization. He was admitted to the emergency room unresponsive, cyanotic, and apneic. Soon after admission he experienced a grand mal seizure and Dopram® and Valium® were administered to control the convulsions. Two and one-half hours after admission, the patient awakened, looked about, and moved all extremities. He breathed on command but not spontaneously, and without a respirator he became cyanotic and apprehensive. He expired approximately 20 h after admission to the hospital.

Pathology—The trachea and bronchi were filled with pink, foamy, edema-like fluid. Both the lungs and liver revealed congestion and the lungs were severely edematous.

Toxicology—See Table 3.

Case 4

A 44-year-old female with a history of alcoholism and emotional instability was found in full rigor. A suicide note was found by the body along with two empty prescription containers. One had contained Valium® and the other Darvon.® The evidence was strong that almost 2 g of Darvon® had been ingested.

Pathology—The lungs showed marked edema and congestion.

Toxicology—No diazepam® was found in the tissues analyzed. See Table 3.

Case 5

A 41-year-old female with a history of alcoholism and severe back pain had been prescribed Darvon® by an orthopedic surgeon. She called her physician and stated that she had taken 20 Darvon® capsules. The physician rushed to her home and called for an ambulance. She arrived at the hospital approximately 1½ h after the ingestion in an unresponsive state and died soon thereafter.

Pathology—The lungs were moderately congested.

Toxicology—A blood alcohol level of 0.43 percent was found in the postmortem sample. See Table 3.

Case 6

A 17-year-old male ingested 25 propoxyphene capsules over a period of 4 h. He suffered severe convulsions followed by collapse and was taken to the hospital. He died soon after admission and it is estimated that the time from the convulsions until death was less than one hour.

Pathology—Moderate congestion of the lungs and marked congestion of the liver, spleen, and pancreas were found.

Toxicology—See Table 3.

Case 7

A 36-year-old female committed suicide following a long period of despondency. A note was found at bedside. She had access to approximately 3.2 g of Darvon® and the bottle was found empty by her bed.

Pathology—Moderate pulmonary and cerebral edema.

Toxicology—See Table 3.

Case 8

A 55-year-old male was found dead in bed. According to medical history, the decedent had suffered an injury 2 years prior to death which had resulted in partial paralysis and considerable pain. During that time he had required up to 5 propoxyphene capsules daily

for pain. Additionally, he had a long history of alcoholism. Judging from the date of the last medication prescribed, the decedent took approximately 3.4 g within a period of 6 h.

Pathology—In addition to moderate edema of the viscera, vertebral fractures suffered 2 years prior to death and cirrhosis of the liver were noted.

Toxicology—See Table 3.

Case 9

A 43-year-old invalid was found dead in bed. He had suffered much pain for years due to a disabling hip fracture. In addition, he suffered from diabetes and epileptiform seizures. His medication had been placed by bedside for convenience. The Darvon® container contained 100 capsules when placed by his bedside; 31 remained when the body was found the following morning.

Pathology—Severe visceral congestion and edema.

Toxicology—Phenobarbital was found in addition to propoxyphene. See Table 3.

Discussion

According to investigators from the Eli Lilly Company [*18*] manifestations of accidental or intentional overdosage with propoxyphene are similar to those of narcotic overdosage and include convulsions, coma, respiratory depression, and circulatory collapse. Postmortem examination of fatal cases may only show pulmonary edema as the significant pathological finding as indicated by Bogartz and Miller [*2*]. This is a nonspecific finding common to drug-induced or drug-related deaths and offers little help to the toxicologist in pinpointing the toxic agent.

Several investigators have analyzed plasma following oral doses of propoxyphene. Wolen et al [*6*] found the mean maximum plasma concentration following oral doses of 65 mg in man to be 6.0 μg/100 ml of plasma. They state that higher concentrations would be expected to have a toxic effect and the concentration of propoxyphene in blood or plasma has a direct relationship to the dose administered. McBay et al [*15*] found plasma concentrations in man reached a maximum of 0.02 mg/100 ml 1 h following an oral dose of 195 mg.

The acute toxicity of oral and parenteral doses of propoxyphene hydrochloride was studied by Emmerson et al [*19*] in mice, rats, and dogs. They reported LD^{50} values in the mouse, rat, and dog were 28, 15, and 29 mg/kg intravenous, and 282, 230, and 100 mg/kg orally. Cann et al [*20*] reported the orally administered median lethal dose of propoxyphene in rats as 273 mg/kg and in mice as 185 mg/kg.

Reports from the literature have indicated that the lethal dose in humans may be much lower than that established in laboratory animals. Our studies further indicate that this is probably the case. Karliner [*21*] reported the case history of a 65-year-old female who died nine days after ingesting 2.3 g (35 mg/kg) of propoxyphene hydrochloride. She was admitted to hospital about 1 h after the ingestion, pulseless and without obtainable blood pressure. The propoxyphene concentration at the time of admission was 0.97 μg/ml of serum. Frasier et al [*22*] reported a case involving a 12-month-old child who ingested 70 mg/kg and died in spite of medical treatment. Bogartz and Miller [*2*] recently presented case data involving two fatalities. The first was an 18-year-old male brought to the emergency room in coma who had written a suicide note and then ingested 3520 mg of propoxyphene (42 mg/kg). The patient failed to respond to therapy. A postmortem blood concentration of 1.1 mg/ml of blood and 9.0 mg/100 g of liver was reported. The second case was that of a 23-year-old female who ingested 1800 mg of propoxyphene (33 mg/kg)

and was dead on arrival at the hospital. In the nine cases analyzed in our laboratories in which the dosage was known, fatal dosage ranged from 15–65 mg/kg (Table 3).

Summary

Toxicological data are presented from fatal cases in which propoxyphene was determined to have caused death or contributed to death. In fatal cases in which only propoxyphene was found, blood levels ranged from 0.1–6.0 mg/100 ml; liver levels ranged from 0.5–55.0 mg/100 g. In many cases multiple drugs, including alcohol, were found and chemical findings from these cases are also presented.

References

[1] Miller, R. R., Feingold, A., and Paxinos, J., "Propoxyphene HCl, A Critical Review," *Journal of the American Medical Association*, Vol. 213, 1970, pp. 996–1006.
[2] Bogartz, L. J. and Miller, W. C., "Pulmonary Edema Associated with Propoxyphene Intoxication," *Journal of the American Medical Association*, Vol. 215, 1971, pp. 259–262.
[3] Young, D. J., "Propoxyphene Suicides, Report of Nine Cases," *Archives of Internal Medicine*, Vol. 29, 1972, pp. 62–66.
[4] Worm, K., "Determination of Dectropropoxyphene in Organs from Fatal Poisoning," *Acta Pharmacologica et Toxicologica*, Vol. 30, 1971, pp. 330–338.
[5] Tennant, F. S., "Drug Abuse in the U.S. Army, Europe," *Journal of the American Medical Association*, Vol. 221, 1972, pp. 1146–1149.
[6] Wolen, R. L., Gruber, C. M., Keplinger, G. F., and Scholz, N. E., "Concentration of Propoxyphene in Human Plasma Following Oral, Intramuscular, and Intravenous Administration," *Toxicology and Applied Pharmacology*, Vol. 19, 1971, pp. 480–492.
[7] Finkle, B. S., "Propoxyphene," *CRC Manual of Analytical Toxicology*, Irving Sunshine, Ed., Cleveland, 1971, pp. 290–292.
[8] Colchin, J. and Daly, J., "Rapid Identification of Analgesic Drugs in Urine with Thin Layer Chromatography," *Experientia*, Vol. 18, 1962, pp. 294–299.
[9] Sunshine, I., "Use of Thin Layer Chromatography in the Diagnosis of Poisoning," *American Journal of Clinical Pathology*, Vol. 40, 1963, p. 576.
[10] Davidow, B., Lipetri, N., and Quame, B., "A Thin Layer Chromatographic Screening Test for the Detection of Users of Morphine and Heroin," *American Journal of Clinical Pathology*, Vol. 46, 1966, p. 58.
[11] Brodie, B. B., Underfriend, S., and Dill, W. J., "The Estimation of Basic Organic Compounds in Biological Material," *Journal of Biological Chemistry*, Vol. 168, 1947, pp. 335–339.
[12] Wallace, J. E., Biggs, J. D., and Dahl, E. U., "A Rapid and Specific Spectrophotometric Method for Determining Propoxyphene," *Journal of Forensic Sciences*, JFSCA, Vol. 4, 1965, pp. 179–191.
[13] Wallace, J. E., Ladd, S. L., and Blum, K., "Determination of Propoxyphene in Biological Materials by Ultraviolet Spectrophotometry and Gas Chromatography," *Journal of Forensic Sciences*, JFSCA, Vol. 16, 1972, pp. 164–173.
[14] Thompson E., Villaudy, J., Plutchak, L. B., and Gupta, R. C., "Spectrometric Determination of d-Propoxyphene (Darvon) in Liver Tissue," *Journal of Forensic Sciences*, JFSCA, Vol. 15, 1970, pp. 605–609.
[15] McBay, A. J., Turk, R. F., Corbett, B. W., and Hudson, P., paper given at the Sixth International Meeting of Forensic Sciences, Edinburgh, September 1972.
[16] Manno, J., Jain, N., and Forney, R., "A Simple Method for the Determination of Propoxyphene in Plasma," *Journal of Forensic Sciences*, JFSCA, Vol. 15, 1970, pp. 158–162.
[17] Emmerson, J. L., Wells, J. S., and Anderson, R. C., "Studies on the Tissue Distribution of d-Propoxyphene," *Toxicology and Applied Pharmacology*, Vol. 11, 1967, pp. 482–488.
[18] *Darvon, Management of Overdosage*, Eli Lilly and Company, Indianapolis, 1970.
[19] Emmerson, J. L., Gibson, W. R., and Anderson, R. C., "Acute Toxicity of Propoxyphene Salts," *Toxicology and Applied Pharmacology*, Vol. 19, 1971, pp. 445–451.
[20] Cann, H. M., and Ver Hulst, H. L., "Convulsions as a Manifestation of Acute Propoxyphene Intoxication," *American Journal of Diseases of Children*, Vol. 99, 1960, pp. 380–382.
[21] Karliner, J. S., "Propoxyphene Poisoning," *Journal of the American Medical Association*, Vol. 199, 1967, pp. 1006–1009.
[22] Frasier, S. D., Crudo, F. S., and Johnson, D. H., "Dextropropoxyphene HCl Poisoning in Two Children," *Journal of Pediatrics*, Vol. 63, 1963, pp. 158–159.

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