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Propoxyphene in Postmortem Toxicology 1976-1978

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ABSTRACT: A total of 1859 cases provides the basis for this study in which propoxyphene, and often its major metabolite, was demonstrated by toxicological analysis in the blood or tissues of the deceased at 27 medical examiner or coroner's offices across the United States and Canada. The study period includes the last five months of 1975 through December 1978. The cases describe a clearly defined adult population with a marked tendency toward hypochondria, chronic minor illness, and severe psychiatric problems. The high proportion of suicides (44.1% of the total cases and 54.0% of the drug-caused deaths) and multiple-drug toxicities (88.6%) suggests that the involvement of propoxyphene in many of these fatalities may be of less significance than the phenomenon of "polypharmacy" and self-medication without appropriate medical supervision. This evaluation of propoxyphene provides no evidence that propoxyphene is responsible for "street-drug" fatalities. Its appearance in postmortem toxicological examinations has been declining sharply since 1977, but it continues to be dangerous when used excessively, particularly in combination with alcohol and other central nervous system depressant drugs.

KEYWORDS: toxicology, propoxyphene

Beginning in the early 1970s, propoxyphene was mentioned with increasing frequency in reports of drug-associated deaths. These were usually single case reports or case summaries from medical examiner jurisdictions [*1-7*]. A larger-scale appraisal of the nature and extent of propoxyphene-associated deaths, employing uniform criteria in 18 medical examiner jurisdictions, was undertaken by the Center for the Study of Human Toxicology, University of Utah, for the period 1970-1975 [*8*]. Since this report other papers have been published that corroborate the findings [*9-11*].

Renewed debate[6] over the nature of propoxyphene misuse in late 1978 and early 1979 em-

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[6]U.S. Senate Select Committee on Small Business Hearings, January 1979, and Food and Drug Administration Drug Abuse Advisory Committee, February 1979.

phasized the need for reliable information on current trends in propoxyphene-associated deaths. The Center reviewed data from medical examiners on a limited basis for the period 1975-1978 from 20 jurisdictions, including all 18 jurisdictions studied in the 1976 report. This limited review was the first to indicate the decreased frequency of propoxyphene-associated deaths following a peak in 1975-1977.

Subsequently, in 1979, the Center began a comprehensive update of the 1976 study, employing uniform criteria as before. The following report, covering the period 1975-1978, is the product of this most recent effort, which is part of a continuous survey that began in 1969. Case totals for 1979 are included but do not form part of the data base analyzed.

Materials and Methods

During the first six months of 1979, 26 medical examiner or coroner offices across the United States (Table 1) were visited. These offices are responsible for investigating unexplained deaths in city-county or state jurisdictions and encompass both urban and rural populations. The combined United States jurisdictional population of these sites totals 56.5 million people, approximately 27% of the current U.S. population. In addition to the U.S. sites, the forensic science laboratory for the province of Ontario, Canada, was visited, which resulted in a combined population covered by all 27 survey sites of 64.8 million people.

Visits of one or two days were made at each site to determine the frequency with which propoxyphene was encountered at that site during the years 1976, 1977, and 1978. Personnel were interviewed concerning the investigative approaches used in the different types of propoxyphene-associated deaths and the current and past analytical toxicology methods employed. Following the interviews, the individual case files of deaths involving propoxyphene at that site were examined and the answers to specific questions concerning medical history, circumstances of death, medicolegal autopsy and toxicology and certified disposition of the case were recorded. Only that information pertinent to the study was recorded and in a manner that ensured the anonymity of the deceased and others associated with the case. No judgments were made by the authors concerning the investigation and final disposition of any case.

At the conclusion of the data-gathering phase, nearly 2000 propoxyphene-associated cases had been examined. The survey attempted to draw a representative portrait of the combined case experience at the 27 sites over the years 1976-1978. Not all deaths in which propoxyphene was suspected were automatically included in the survey. Only those cases in which propoxyphene or its metabolites were unequivocally shown by postmortem toxicological analysis to be present in the deceased were considered; of these, only well-documented cases with either full investigation histories or cases in which it was thought by the pathologist and toxicologist that the presence of propoxyphene had played a significant role in the death were selected. As a consequence of this selection process, the survey data should not be used as a measure of the overall incidence or frequency of this drug at the survey sites. From the 2000-case total, 1859 cases contained information sufficient for inclusion. These 1859 medical examiner and coroner cases serve as the data base and foundation for the correlations, associations, and conclusions in this report.

Although propoxyphene was not the proximate cause of all 1859 deaths, every case surveyed had propoxyphene or its major metabolite, norpropoxyphene, demonstrated in blood or tissues of the deceased by toxicological analysis at the survey site. The proportion of the 1859 cases used to construct tables and graphs and from which conclusions were drawn is noted in the report in each instance. However, 81.7% of the total cases surveyed had drugs mentioned by name in the cause-of-death statement of the death certificate, and of these 52.3% (794 cases) mentioned propoxyphene specifically. Only 13.3% of the cases were classified on the death certificate as homicides, natural deaths, or unknown cause at the time of the survey.

TABLE 1—*Survey sites and population.*

	Site	Site Code	Jurisdictional Population, Millions (1978)
1	Los Angeles County, Calif.	LA	7.0
2	North Carolina (State)	NC	5.6
3	Georgia (State)	G	5.5
4	Cook County (Chicago), Ill.	IL	5.5
5	Maryland (State)	MD	4.0
6	Minnesota (with St. Paul but excluding Minneapolis)	MIN	4.0
7	Wayne County (Detroit), Mich.	WCD	2.7
8	Philadelphia (City and County), Pa.	PH	1.9
9	Orange County, Calif.	OC	1.8
10	Allegheny County (Pittsburgh), Pa.	ACP	1.8
11	San Diego (City and County), Calif.	SD	1.7
12	Dade County (Miami), Fla.	MI	1.5
13	Phoenix (Maricopa County), Ariz.	MC	1.3
14	Utah (State)	UT	1.3
15	Dallas (City and County), Tex.	DA	1.2
16	New Mexico (State)	NM	1.1
17	Erie County (Buffalo), N.Y.	BE	1.1
18	Oakland (Alameda County), Calif.	AC	1.0
19	Rhode Island (State)	RI	1.0
20	Northern Virginia	NV	1.0
21	Shelby County (Memphis), Tenn.	MT	0.9
22	Bexar County (San Antonio), Tex.	SAT	0.9
23	Washington, D.C.	WDC	0.8
24	Nassau County, N.Y.	NY	0.8
25	San Francisco (City and County), Calif.	SF	0.7
26	Las Vegas (Clark County), Nev.	LV	0.4
Total U.S. population surveyed			56.5
27	Toronto and Province of Ontario, Canada	TOR	8.3
Survey total			64.8

The individual survey sites, the population of their jurisdictional areas, and the number of propoxyphene-associated cases collected at each are given in Tables 1 and 2. The populations of the sites range from 400 000 in Clark County, Nevada (which includes the city of Las Vegas), to 8.5 million in Toronto and the remainder of the province of Ontario. The site with the largest population in the United States was Los Angeles County, with 7.0 million people. Table 2 clearly shows the annual trend of cases from the beginning of the earlier study through the current period. Case totals for 1979 were available by the time this report was in preparation and are, therefore, included in the table, but they do not form part of the data base for analysis.

Results

Propoxyphene Cases by Year

When the survey cases are analyzed by year, as shown in Table 2 and Fig. 1, it can be seen that the combined case experience at all 27 sites underwent an unmistakable annual increase from 1972 (the first year in which all suitable, well-documented cases from all sites were collected) through 1977. The number of propoxyphene-associated deaths declined sharply

TABLE 2—*Number of propoxyphene-associated cases.*[a]

Site	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	Total
LA	...	...	...	37	33	63	55	101	121	64	32	286
NC	2	3	2	21	21	30	50	34	36	31	18	101
G	...	1	2	5	6	6	7	10	15	6	11	31
IL	...	...	...	...	...	...	...	...	48	44	18	92
MD	...	...	...	...	...	...	56	46	58	65	31	169
MIN	...	...	...	1	2	3	3	1	4	0	0	5
WCD	...	...	...	8	12	31	42	29	30	27	26	86
PH	...	...	...	25	22	28	18	26	29	28	17	83
OC	...	...	...	8	12	15	17	19	26	14	13	59
ACP	...	...	...	...	...	...	...	8	4	4	...	16
SD	...	...	...	20	24	23	25	28	30	21	14	79
MI	...	...	...	2	13	10	19	6	14	11	3	31
MC	...	...	...	...	...	...	...	17	20	15	6	52
UT	...	...	...	...	7	11	5	17	18	17	3	52
DA	...	...	...	14	10	16	27	12	19	16	14	47
NM	...	...	...	...	4	8	19	12	10	11	5	33
BE	...	...	...	...	...	...	...	17	13	7	10	37
AC	...	3	3	3	9	11	5	9	20	10	10	39
RI	...	...	...	...	...	...	...	16	19	10	6	45
NV	...	...	...	...	...	...	...	10	4	6	11	20
MT	...	...	...	...	...	...	...	8	7	6	2	21
SAT	...	...	...	...	...	...	...	11	8	8	4	27
WDC	...	...	...	...	...	...	...	6	3	2	7	11
NY	...	...	...	...	...	...	...	14	16	3	12	33
SF	...	...	...	...	...	...	...	19	16	15	12	50
LV	...	...	...	2	1	2	7	6	10	1	1	17
U.S. totals	2	7	7	146	176	257	355	482	598	442	286	1522
TOR	...	...	...	44	39	46	42	77	113	111	83	301
Survey totals	2	7	7	190	215	303	397	559	711	553	369	1823[a]

[a]The total base for the report is 1859 cases, 1823 cases from 1976–1978 and 36 cases from the last quarter of 1975; ... = no data available and 0 = no cases that year.

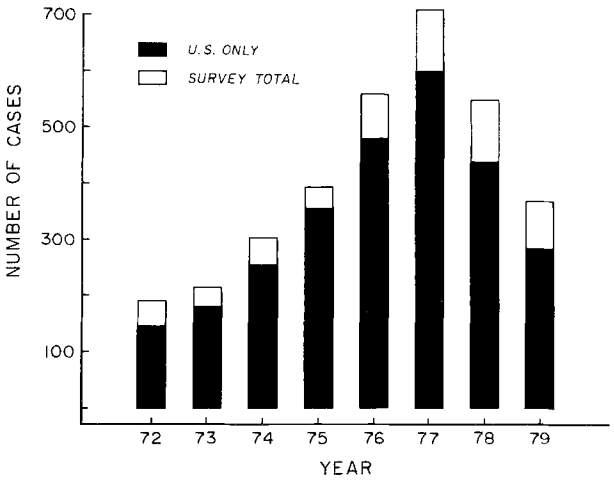

FIG. 1—*Annual totals of propoxyphene cases.*

following their peak in 1977. If the number of cases recorded in 1979, one year beyond the end of the survey period, is included, a continuous, steep decline in the number of propoxyphene-associated deaths is evident. The incidence of propoxyphene cases decreased by 22% from 1977 to 1978 and by 33.3% from 1978 to 1979. Inspection of the case numbers for each site shown in Table 2 indicates that at every site the number of propoxyphene cases has either reached a plateau or is declining.

Because the analytical methods used for screening at each of the sites were constant or improved during 1976–1978, an increase in reported propoxyphene cases was anticipated. In addition to improved laboratory capability, there was a heightened concern among physicians and medical examiners about potential propoxyphene problems that could have resulted in a greater proportion of cases being screened for propoxyphene. When these circumstances are considered, the decrease in occurrence of the drug in postmortem cases is striking.

One explanation might be that the decline is directly proportional to a reduced availability or sales of the drug. An analysis of the DAWN reports (the federal Drug Abuse Warning Network) and medical examiner cases as of February 1980 indicates a rapid decline in cases, and it has been shown that the rate of decline of propoxyphene-associated cases is greater than the decrease in new prescriptions for the drug; that is, death cases are declining faster than prescription volume [*12*].

Characteristics of the Deceased

Although the age range extended from less than 10 years to greater than 65 years, it was predominantly a young adult population. The peak age group was 21 to 30 years and accounted for 31% of all the cases. Males outnumbered females by a factor of 1.4. In 94% of the cases surveyed deaths occurred between the ages of 20 and 40 years. It is noteworthy that only about 35% of the U.S. population falls within this age group, and that this group suffers the highest incidence of suicide.[7] There was a very small number in the older age brackets despite the fact that geriatric patients account for about one third of propoxyphene prescriptions. The adolescent and pediatric populations were nearly nonexistent. The distribution of the sexes for the total survey is equivalent to the national average of 1.06.

Information on the racial distribution of the deceased was available in all of the 1859 cases; however, the survey population resembled the general U.S. population closely. Similarly, the various occupations held by the deceased at or near the time of their death were also tabulated. This information was available for only half of the cases, but no group was overrepresented when compared with general population. Most of the deceased were white, middle-class, blue-collar workers.

Death occurred at home or at the residence of a friend or relative in almost three fourths (71%) of the cases, usually in or on a bed, a couch, or on the bathroom, kitchen, or living-room floor. Only 1.5% were in automobiles, and virtually none died in hotels/motels.

Of the total 1859 cases, 824 (44.6%) had a known previous medical history as defined by the categories in Table 3. These 824 cases presented more than a thousand specific complaints or medical conditions. While a previous history of injury or chronic illness stands out as the most frequently encountered specific category, it represents only about one third of all the categories, and when considered on a case basis, occurred in only 15.5% of the total survey fatalities. The largest class consisted of many nonspecific, minor, common painful ailments, and although as a group they accounted for nearly 20% of the total, no one entity within the class predominated.

In an effort to define the overall mental and emotional condition of this population near the time of death, this aspect of their medical history was documented when reliably known.

[7] "Statistical Abstract of the United States," National Library of Medicine, Washington, D.C.

TABLE 3—*Preterminal medical history.*

Medical History	Cases,[a] %
Recent injury or chronic illness	35.0
Recent hospitalization	17.0
Cardiovascular	14.2
Recent surgery	11.0
Gastrointestinal	9.3
Drug abuse treatment	7.8
Other, nonspecific, and miscellaneous	5.7
Total	100.0

[a]Based on 824 cases (44.6% of total cases).

Psychological stability is a difficult parameter to evaluate retrospectively, particularly when based on such things as police reports and investigator interviews with friends and relatives. Because of these obvious limitations, great care was exercised in judging this category and if any bias exists it is toward a conservative view. Approximately 59% of the entire survey population had a documented history of emotional disturbances or drug-abuse problems. This accounted for 1097 cases, which represented 1623 separate "occurrences" from the total survey. This does not represent 1623 cases, as it was possible for one case to have occurrences of more than one type. A history of being clearly and unusually despondent at or near the time of death was the most prevalent category and accounted for 21% of the occurrences. A significant number of these patients, 12.0%, were undergoing psychiatric treatment at the time of death. In addition, almost 10% had previously attempted suicide.

Propoxyphene as a Drug of Abuse

Table 4 highlights those cases in which there was a previous drug-abuse history; again, these are conservative estimates. A current or past history of heroin abuse was known in only 91 cases, a very low number when compared with the number of heroin fatalities as a proportion of deaths from all other drugs. The only other categories of notable size are those of alcohol abuse or misuse, 16.2%, and a nonspecific drug abuse that generally represented a mixed-drug abuse, often including barbiturates, other sedative-hypnotics, and tranquilizers. Cases with a confirmed history of propoxyphene abuse were quite infrequent, being reported in only 33 cases (1.7%). As indicated in Table 4, these data are consistent with the 1972–1975 figures. There is no evidence to suggest that the deceased were a part of the street-drug-abuse population, and these observations do not support the notion that propoxyphene is frequently associated with opiate narcotic abuse. The chief problems remain alcohol and self-medication with multiple drugs. Eighteen percent of the total survey population had a history of using multiple drugs without appropriate medical supervision. Although the origin of the propoxyphene was known for only 41.2% of the cases, it was almost always obtained by medical prescription, either for the deceased or for a friend or relative of the deceased. The drug was obtained illicitly in less than 0.5% of the cases. In only four cases was the drug known to have been injected intravenously. These facts, together with the finding that in 85.4% of the known cases the drug was ingested orally, support the view that the cases surveyed do not represent a drug-abuse population.

Although the napsylate salt of propoxyphene has been used in the management of selected cases of heroin dependence, only 0.7% of the deceased were undergoing methadone and associated therapy. Three and one half percent of the total cases had a history of some treatment for drug abuse. Propoxyphene in various proprietary forms was prescribed as an adjunct to drug-abuse treatment in only nine cases.

TABLE 4—*Cases involving a history of drug misuse.*

History	1975–1978 Cases, *n*	1972–1975 Percentage of All Cases Surveyed[a]	1975–1978 Percentage of All Cases Surveyed[a]
Alcohol or drug abuse, or both	743	34.3	39.2
Drug misuse	334	17.1	18.1
Alcohol abuse only	300	17.0	16.2
Heroin abuse	91	3.3	4.9
Propoxyphene abuse	33	1.6	1.8

[a]Percentage values do not tally because of overlap between categories.

Occurrence of Propoxyphene, Alcohol, and Other Drugs

Of the 1859 cases, 336 (18.1%) involved propoxyphene only; 326 (17.5%) involved propoxyphene and alcohol only, but 1523 (81.9%) contained propoxyphene and at least one other drug, including alcohol. These statistics are consistent with the figures for 1972–1975; however, there was a decrease of 5.8% for propoxyphene-only cases.

In nearly two thirds of the deaths, 60%, it was known from the scene investigation, before the autopsy and toxicology examination, that propoxyphene had been available to the deceased. In 40.7% of these cases, Darvon® was the proprietary form mentioned (9.8% being Canadian preparations). The only noteworthy difference from the earlier 1972–1975 survey was the increased proportion of napsylate forms of propoxyphene, which now dominate the propoxyphene market.

Alcohol was detected in 49.2% of the cases and was the drug most frequently present in addition to propoxyphene. Its occurrence increased by 7.2% over the 1972–1975 survey, and it remains of major toxicological concern in forensic science cases, particularly when other drugs are present in combination, a condition that was very common in the study population. Sixteen and two tenths percent of the deceased had a documented history of alcohol abuse or alcoholism. Figure 2 illustrates that most of the blood-alcohol concentrations (BAC) were significant. Although about 20% of the cases in which the BAC was determined were between 0.05 and 0.10% and could be generously interpreted as social drinking, fully 48% were in the range of 0.10 to 0.25%, that is, very heavy, habitual alcohol users. In spite of the fact that alcohol was the most frequently occurring other drug, there were a large number of other medications, in addition to propoxyphene, known to be available to the deceased.

There are two sources of evidence for the involvement of other drugs in the survey cases: "drugs known to be available to the deceased" from observations made at the scene of death and "drugs detected by toxicological analysis" during the postmortem laboratory studies. There were 1746 cases in which there was evidence that other drugs in addition to propoxyphene were available to the deceased. In 71.9% of these cases, other drugs in addition to the propoxyphene and alcohol were confirmed by laboratory analysis.

Table 5 lists those drugs that occurred most frequently in combination with propoxyphene. Diazepam, in its various dosage forms, was available to the deceased in 443 cases (25.4% of the cases). Toxicological analyses demonstrated the presence of this drug in 376 of the survey deaths. In contrast to the presence of diazepam, there were only 97 cases in which chlordiazepoxide preparations occurred and even fewer cases in which this drug was shown by analysis to have been ingested by the deceased. The high frequency of the apparent availability of flurazepam (158 cases) and its relatively low confirmation by analysis (51) are significant because it is a potent benzodiazepine sedative-hypnotic rapidly metabolized and

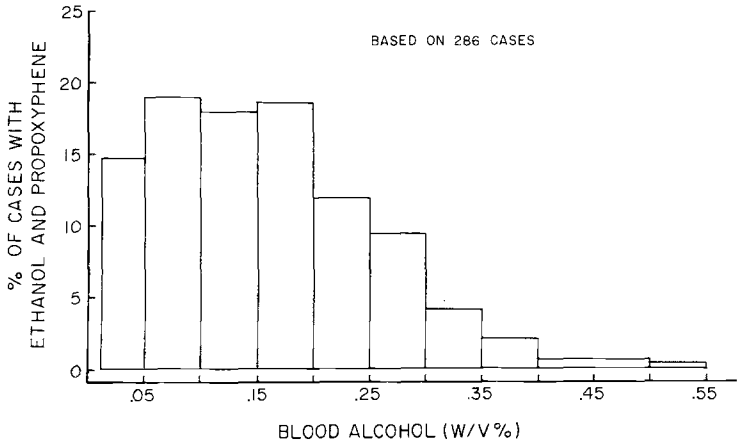

FIG. 2—*Alcohol-frequency distribution for cases having only alcohol and propoxyphene.*

TABLE 5—*Most frequently occurring medications, other than propoxyphene and alcohol, known to be available to deceased at time of death.*

Medication	Cases[a]	
	n	%
Diazepam (Valium®)	443	25.4
Flurazepam (Dalmane®)	158	9.0
Chlordiazepoxide (Librium®)	97	5.6
Phenobarbital	70	4.0
Amitriptyline (Elavil®)	59	3.3
Secobarbital (Seconal®)	55	3.2

[a]Based on 1746 cases. Percentages do not tally because of overlap of cases.

very difficult to detect and assay in blood and tissues. Illicit drugs and the "Miscellaneous" categories in Table 6 were composed of a variety of agents, none of which alone was found with significant regularity.

Cause and Manner of Death

Almost all of the cases included in the survey were, of course, drug-caused deaths. In 1519 cases (81.7% of the total survey) drug involvement was recorded as part of the official cause-of-death statement. In 973 cases propoxyphene was regarded as contributing to the cause of death. The remainder generally involved physical injuries, including gunshot wounds, automobile fatalities, hanging, electrocution, or, more often, natural diseases.

The most frequent manner of death was suicide; of the total 1859 cases surveyed, 820 (44.1%) were classified as suicide, or 54% of the 1519 cases that were drug-caused deaths. This is particularly important because there is general agreement that suicides are under-reported, perhaps by as much as 100% [*13*]. They are rarely identified as such unless the evidence is very strong. Table 7 presents the manner-of-death statistics.

If only suicide cases are considered, propoxyphene alone accounted for 142 cases, pro-

TABLE 6—*Drug classes detected by toxicological analysis.*[a]

Drug Class	Number of Cases
Antianxiety agents	505
Analgesics, nonnarcotic	369
Sedative-hypnotics	
Barbiturates	317
Nonbarbiturates	203
Analgesics, narcotics	219
Antidepressants	140
Antipsychotics	53
Antihistamines and decongestants	37
Muscle relaxants	31
Miscellaneous agents	24
Anticonvulsants	23
Local anesthetics (Lidocaine®)	21
Illicit drugs	16
Stimulants and anorectics	14

[a]Excluding ethanol and propoxyphene.

TABLE 7—*Manner of death.*[a]

Category	1975–1978 Cases, *n*	1972–1975 Percentage of All Cases Surveyed	1975–1978 Percentage of All Cases Surveyed
Suicide	820	45.8	44.1
Accident	458	26.1	24.6
Undetermined	333	20.8	17.9
Natural	175	6.2	9.4
Homicide	32	...	1.7
Not known	41	...	2.2
Total	1859		

[a]The study period includes the last five months of 1975 through 1978.

poxyphene and alcohol 134 cases, and propoxyphene together with other drugs 544 cases, more than two thirds of the suicides. The majority of suicidal drug overdoses involving propoxyphene, therefore, continue to be multiple-drug intoxications, with other drugs present often at very high, toxic, or lethal concentrations.

Records from the individual death investigations showed that in 598 cases (32.2%) the behavior of the deceased before death gave some indication of suicidal intent: the presence of a suicide note, 184 cases; specific statements to relatives or acquaintances, 193 cases; previous suicide attempts, 217 cases; or obvious actions indicating intent (such as slashing of wrists), 134 cases. Not all of the total 598 deaths with circumstantial evidence of suicide were eventually certified by the medical examiner or coroner as such; some were still classified as accidents or deaths of undetermined manner. In these cases there were sometimes other indications that suicide was not the actual intent but was only a gesture or an attention-seeking action that had gone too far, or there were other facets of the case that opposed the apparent suicidal evidence. In any event, it continues to be certain that the suicide rate is underreported and that medical examiners and coroners are very reluctant to assign that designa-

tion without unimpeachable evidence. One consequence of this conservatism is an exaggeration of the undetermined, accident, and even the natural-death reports.

A major conclusion of this study is confirmation of the opinion, founded previously on the 1972–1975 report, that this deceased population consists mainly of victims of multiple-drug toxicity, propoxyphene being the only common factor, and that alcohol is a particularly dangerous component in any of the many drug combinations. The deceased are predominantly suicides and not unwitting victims of accidental overdose. In one Canadian suicide case the deceased had 24 different drugs available, and in 20 cases at one site, two or more proprietary forms of propoxyphene had been prescribed for the deceased.

Death-Scene Investigation, Terminal Symptoms, and Postmortem Pathology

In nearly 1600 of the 1859 survey deaths a complete and thorough postmortem medical examination was conducted. The majority of the survey cases were investigated within 12 to 24 h of the death. While much of interest can be derived from the survey cases taken as a whole, this and the following paragraphs on the toxicology findings will focus primarily on those cases directly resulting from drug overdosage.

The death-scene investigation can and often does point out the initial line of inquiry to be taken by the forensic pathologist. In 78.5% of the cases (1460), the medical investigator believed from the first that the death was associated with, if not directly caused by, drugs. Estimations of the survival times in the drug-death cases (that is, the interval between when the deceased were known to ingest the drug or were last seen alive and when they were found dead) were not particularly instructive. Obviously, this sort of measurement can only be an estimate because a majority of the deaths occurred in private residences and most victims were already dead when discovered. In consequence, the shorter times, as a whole, are probably more accurate. The longer estimates could, and some undoubtedly do, represent a period in which the deceased were dead but undiscovered. Figure 3 graphically illustrates the distribution of "fatal intervals" for those cases in which only propoxyphene was involved. Approximately 55% of the drug deaths were known to have occurred within 10 h, but nearly 16% of these were "overnight" deaths; that is, the deceased were found dead in the morning but had been seen alive the preceding evening. There was no evidence for an idiosyncratic drug reaction that might be suspected in these cases. As reported in the 1972–1975 study [*8*], almost all of the victims of large propoxyphene overdoses will die in about 8 to 10 h unless they receive prompt medical treatment.

Terminal symptoms were observed and noted in only 377 of the deaths. This information was derived from the medical records of those who had received emergency treatment or from interviews conducted by the investigator at the scene with relatives or acquaintances who described the victim's state just before death. These cases accounted for 459 occurrences of definable symptoms, ranging from coma, the most frequently observed at 56.2%, to seizures, syncope, and vomiting, which were the least observed, each at 5.0% or less. In general, these symptoms appeared to be central nervous system (CNS)-mediated, rather than peripheral, and of a nonspecific depressive type. The prevalence of apparent intoxication (15.6%) and coma agrees, in general, with the clinical description of propoxyphene overdosage reported in the 1972–1975 report [*8*], but these symptoms of intoxication may well have resulted directly from alcohol in many cases. In 25.2% of the cases the terminal event was either cardiac or respiratory arrest, or both, but there was no clear indication to establish a cause-and-effect relationship between these physiological events and the concentrations of propoxyphene and its major metabolite in the body.

Very few of the deceased received emergency medical treatment just before they died. Only 155 received hospital emergency care. In addition to these patients, records indicate another 18 of the deceased received treatment from fire department emergency medical

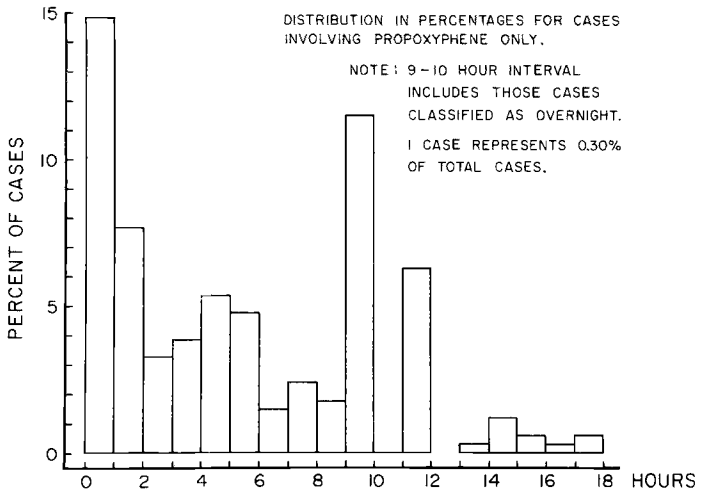

FIG. 3—*Time intervals: last seen alive to death.*

technicians or other paramedical personnel. Of these (141 cases), cardiopulmonary resuscitation or some other form of respiratory assistance was the most common mode of treatment; and lidocaine, naloxone, and vasopressor agents were the most common drugs given.

Gross findings at autopsy in the 1519 fatalities in which deaths were due directly to drugs, and propoxyphene was shown by analysis to be present, revealed nothing that could be considered specific for propoxyphene involvement. The most common observations—pulmonary, visceral, and cerebral edema and congestion—are typical of deaths caused by drugs of the CNS-depressive type, but they are not specific or diagnostic. Evidence of previous intravenous drug use, as indicated by "needle tracks," occurred only 85 times and substantiates the lack of "hard" drug abuse that was apparent from the personal background histories.

The microscopic pathology played no great role in the investigation of these deaths.

Postmortem Toxicology

The only feature common to the 1859 death cases was the presence of propoxyphene or propoxyphene and its primary metabolite, norpropoxyphene, in the blood or tissues of the deceased, as demonstrated by toxicological analysis at the survey site. The primary specimen used for the initial screening at these sites was blood, heart blood being used in about three fourths of the cases.

The screening methods for propoxyphene analysis at the survey sites were diverse, but none of the sites had changed their procedures in the four years prior to this survey. Only three sites used the McBay ultraviolet spectrophotometric assay [*14*] throughout the study period, and one of these changed to gas chromatography (GC) beginning January 1979; five other sites had adopted either GC or GC/mass spectrometry (MS) during the study period. The cases from these sites were segregated according to method when the analytical data were evaluated. The propoxyphene screen almost invariably involved solvent extraction, followed usually by either gas-liquid chromatography (GC) or ultraviolet spectrophotometry (UV) and thin-layer chromatography (TLC). A variety of solvents were employed, but *n*-butyl chloride and diethyl ether were by far the most common. Identification of propoxyphene or its metabolite was accomplished by spectrophotometry after irradiation by UV light, or by GC primarily, but five sites used thin-layer chromatography and eight sites used

GC/MS. At most of the sites internal standards and GC equipped with flame ionization detectors were used. Except for those sites using GC/MS, the GC limit of sensitivity claimed by most of the toxicologists was near or slightly better than 0.2 μg/mL in blood.

In addition to the use of UV and GC for the detection and quantitation of propoxyphene, a number of other techniques that rely on variations of GC/MS have been developed. These include chemical ionization/multiple ion monitoring, with the use of deuterated stable isotopes as internal standards. They have, however, received only limited use in the daily practice of forensic toxicology. The growing concern over the specific detection and accurate assay of all basic drugs that may occur in blood at concentrations lower than 1 μg/mL is certain to cause an increased reliance on these ultrasensitive procedures, particularly new immunological approaches.

A total of 1179 of the survey cases had propoxyphene or norpropoxyphene, or both, quantitated in the blood. To compare the results achieved with the two different methods, UV (153 cases) and GC (1026 cases), and to test for any bias that may be present in one or the other, the blood concentration distributions from the survey deaths were plotted for each of the methods. Figures 4, 5, and 6 show the distributions of blood concentrations as a percentage of the cases quantitated by GC and as a percentage of those assayed by UV. Those cases classified as suicides were separated to determine if there was any shift in the distribution of the concentrations to higher values. Inspection of the figures indicates some support for this but only at concentrations greater than 10.0 μg/mL. In any event, these massive concentrations could have resulted only from very large, suicidal doses. There is a slight tendency for the UV values to be higher, but it is hardly significant. This tendency can be explained partly by the greater proportion of cases in the 1.0 μg/mL category of the GC analyses, a feature of the greater sensitivity of this method, and by the number of UV cases with concentrations greater than 15.0 μg/mL. There is evidence for the belief that quantitation of blood "propoxyphene" by UV in these cases gave higher concentrations because the value includes the norpropoxyphene metabolite. The concentration range for all cases with blood concentrations reported in the survey was from less than 0.1 to greater than 20 μg/mL. The peak frequency shown in all of the figures was in the range of 0 to 1 μg/mL, and these represent 26.2% of the total cases and 22.5% (32) of those cases in which only propoxyphene was involved. Of all the cases, 44.2% had blood concentrations in the range of 0 to 2 μg/mL, and almost three-quarters of the cases were accounted for at 5 μg/mL or less. An even greater

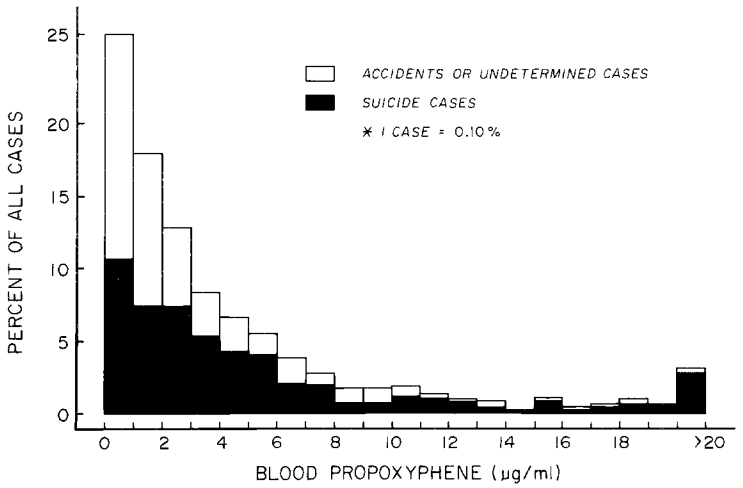

FIG. 4—*Blood propoxyphene distribution for all cases surveyed (analysis by GLC).*

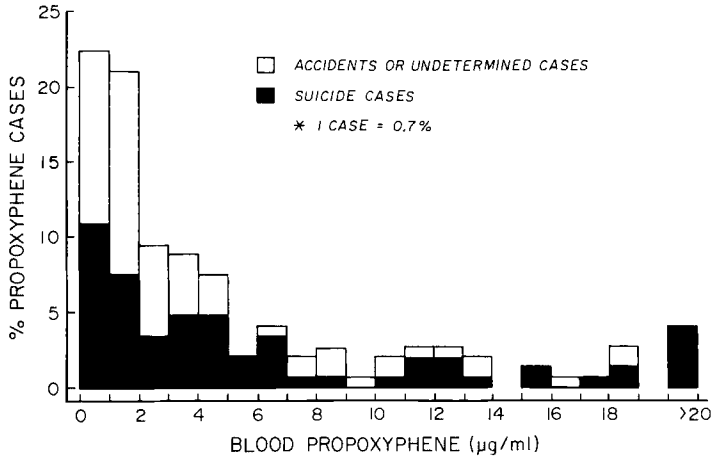

FIG. 5—*Blood propoxyphene distribution for cases containing propoxyphene only (analysis by GLC).*

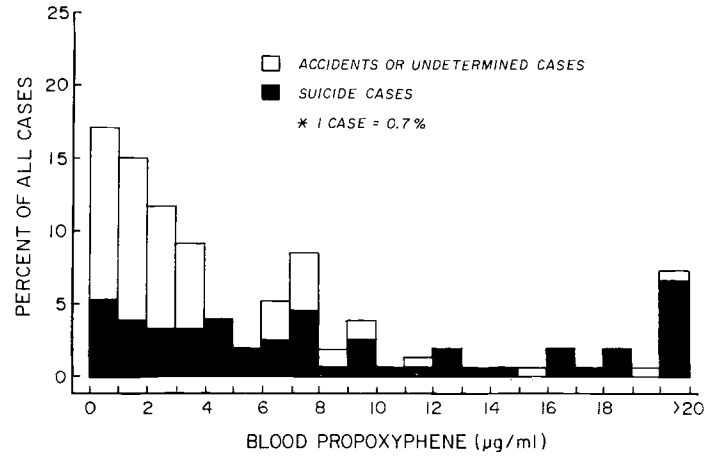

FIG. 6—*Blood propoxyphene distribution for all cases surveyed (analysis by UV).*

proportion of those cases containing only propoxyphene, 90.6%, was accounted for at 5 μg/mL or less.

The distribution of the concentrations in the suicide cases does not differ significantly from that for the total cases. It is different, however, when those cases containing propoxyphene only are inspected. Although most of the concentrations occur at 5 μg/mL or less, there are peak frequencies in the range of 11 to 13 μg/mL and also at greater than 20 μg/mL. This is not surprising, because many suicides ingest massive quantities of the drug; if they live for a few hours before death and continue to absorb the drug from the GI tract, then the circulating blood concentrations can reach very high levels.

In an attempt to analyze further the reasons for fatalities at blood propoxyphene concentrations of less than 1 μg/mL, the frequency of occurrence of alcohol in this segment of cases was examined. There were 58 cases in which only propoxyphene (at less than 1 μg/mL) and alcohol occurred. Fifteen of these cases were either homicides, natural deaths, or primarily

alcohol intoxications. Of the remaining 43 cases, 30 had blood alcohol concentrations between 0.10 and 0.30%, that is, of toxicological significance in combination with the propoxyphene. There were six cases in which the blood propoxyphene concentration was less than 1.0 μg/mL and the alcohol concentration was less than 0.05%, and all of these appeared to be thoroughly evaluated drug-combination deaths.

Very few of the survey cases had complete propoxyphene/norpropoxyphene tissues distribution data determined. Only six laboratories routinely assayed the drug and its metabolite in blood, gastric contents, liver, and urine, although some of them also analyzed a variety of additional tissues. Most of the laboratories did, however, assay liver tissue for at least propoxyphene. No attempt was made to evaluate the toxicological significance of the liver propoxyphene concentrations in this study because this was undertaken and reported in the 1972–1975 survey [*8*], and it was clearly shown that although the liver propoxyphene concentrations were almost invariably greater than those in the blood, there were no useful relationships that could be developed for pharmacokinetic interpretation of the analytical data.

Since the earlier report, analytical techniques for the accurate determination of norpropoxyphene in blood and tissues have become available and can now be applied to cases in which the drug is involved. At the same time some controversy has developed about the potential toxicity of the metabolite, particularly with reference to possible cardiac impairment [*15*], its longer plasma-elimination half-life, and its likely accumulation in the blood to toxic concentrations. There is no reliable evidence of cardiac toxicity associated with propoxyphene ingestion in the study cases, although it is recognized that a hospital population of nonfatal overdose cases might be more revealing in this regard. There were 642 cases in which propoxyphene and norpropoxyphene concentrations were determined in postmortem blood by accurate gas chromatography methods. The concentrations and their distribution as a percentage of the 642 cases are shown in Fig. 7. The profile of concentrations is not dissimilar to that of the parent drug, with 60% of the cases falling at 5 μg/mL or less. In about 7% of the cases the metabolite concentration exceeded 20 μg/mL. Examination of some of these latter cases revealed that they were generally associated with deceased who had been in a long coma before death. There was not, however, any firmly established relationship between the metabolite concentration and the interval between drug ingestion and death.

The appearance of norpropoxyphene in blood at detectable concentrations occurs very rapidly after drug ingestion. Figures 8, 9, and 10 were constructed to examine the relationship between the parent drug and metabolite concentrations in those cases in which both were determined simultaneously. Although in most of the cases the metabolite concentration was greater than the parent propoxyphene, irrespective of variables such as time, the data cannot be used to predict toxicity reliably on the basis of the parent-to-metabolite ratios. The case values depicted in Figs. 8, 9, and 10 do show a tendency to cluster about a mean and it is instructive to appreciate that the ratio norpropoxyphene/propoxyphene for the mean values is not significantly different for the three different populations—for all cases surveyed, 1.30; for multiple drug cases, 1.31; and for cases in which only propoxyphene was ingested, 1.17. In this last instance there was a greater proportion of the parent drug present relative to the mean than was the case in the other two populations. This again belies the idea that norpropoxyphene often accumulates to concentrations greatly in excess of the parent drug and is, therefore, the true culprit.

There were ten cases in which norpropoxyphene was present in the blood but no parent propoxyphene was detected. The concentrations of the metabolite ranged from 0.6 to 4.0 μg/mL. None of the ten cases involved propoxyphene alone, seven were multiple drug intoxications in which other drugs were obviously causative, two were violent homicidal deaths, and one was an accidental drowning in which very high concentrations of alcohol and diazepam were implicated. Both homicide victims sustained fatal gunshot wounds, both severely under the influence of alcohol, one with diazepam (and 4.0 μg/mL norpropoxy-

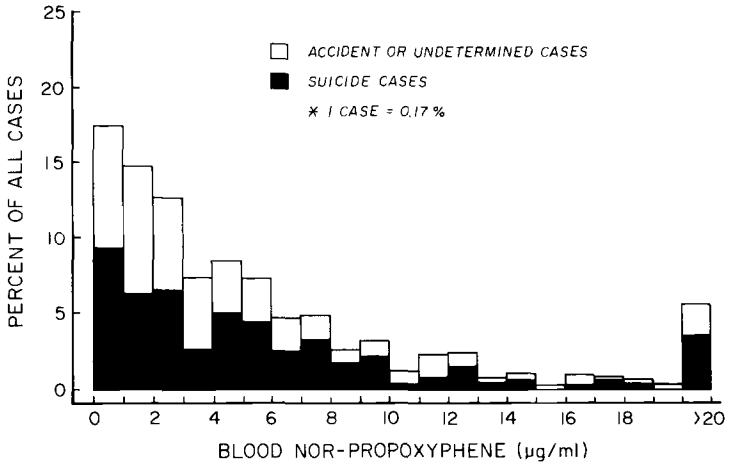

FIG. 7—*Blood norpropoxyphene distribution (analysis by GLC).*

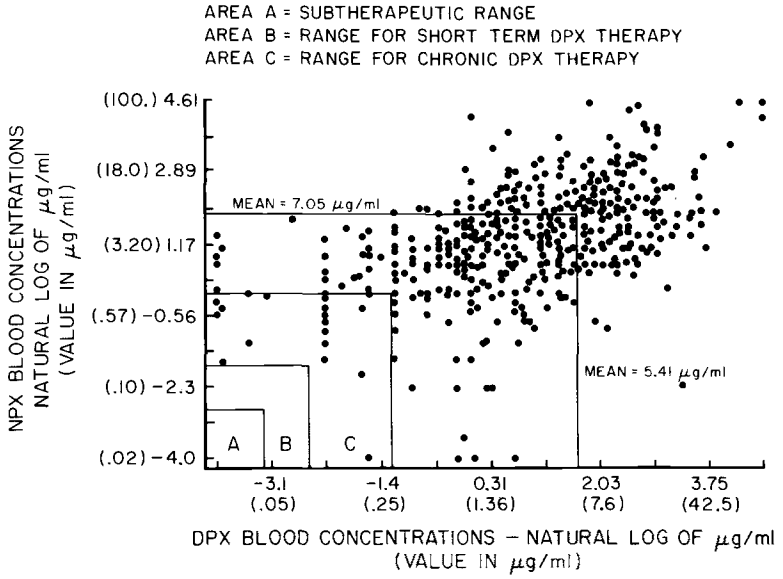

FIG. 8—*Propoxyphene and norpropoxyphene blood concentrations for all cases surveyed (642 cases).*

phene) and one with morphine (heroin). Of the multiple drug deaths, two were overwhelmingly barbiturate intoxications, two were caused by nonbarbiturate sedatives (meprobamate and ethchlorvynol), and three involved alcohol and multiple sedative-hypnotics.

There were 20 cases in the survey in which the quantity of propoxyphene ingested before death was reliably known. These cases were carefully examined to determine if there was a relationship between the dose of the drug, the time interval before death, and the postmortem blood concentration. When these three parameters are evaluated, the data are random and confirm pharmacokinetic principles that blood concentrations cannot be used to calculate retrospectively the quantity of the drug ingested except in a very general way, or the time

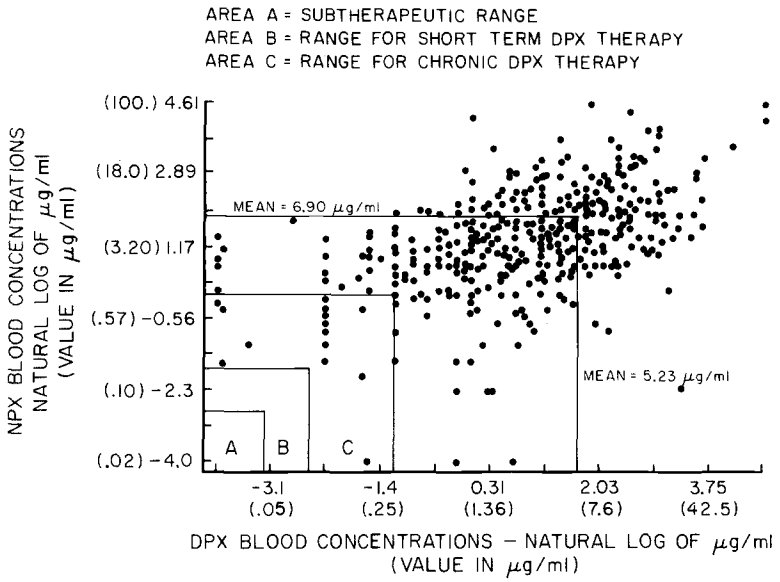

FIG. 9—*Propoxyphene and norpropoxyphene blood concentrations for all cases involving multiple drugs (525 cases).*

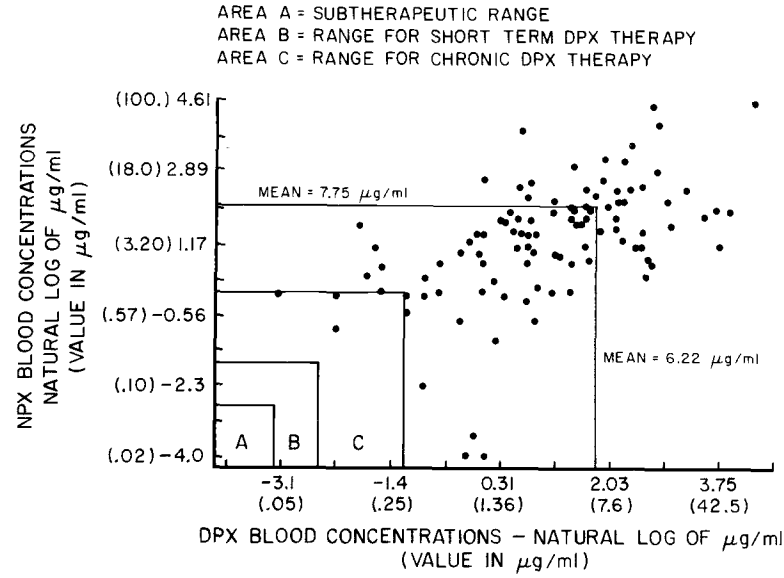

FIG. 10—*Propoxyphene and norpropoxyphene blood concentrations for all cases involving propoxyphene alone (117 cases).*

at which it was taken. It is very tempting to make this calculation in cases where the dose ingested is an important factor, but the attraction and simplicity of the practice should be resisted vigorously. It can only lead to erroneous conclusions and interpretations of the circumstances of death.

In summary, it is evident from the toxicological analyses that most of the deaths in which propoxyphene is significant are associated with concentrations of the drug and metabolite in the blood that are much higher than those achieved during typical analgesic therapy and that are often found together with alcohol or other drugs. These high concentrations, which result from the ingestion of doses far in excess of those recommended for therapeutic purposes, should not be confused with the cases in which low concentrations of propoxyphene are detected but a variety of other potent drugs are also present in the blood and tissues. It is also clear that norpropoxyphene is not the cause of accidental deaths.

Conclusions

The following conclusions are drawn from a total of 1859 cases that met the criteria for inclusion in this study. These consist of 36 cases occurring in the last five months of 1975, 559 in 1976, 711 in 1977, and 553 in 1978. Data on the 369 deaths associated with propoxyphene in 1979 were collected but not analyzed. In each of the 1859 cases the presence of propoxyphene, and often its major metabolite, in the blood or tissues of the deceased was confirmed by toxicological analysis at the survey site.

The incidence of propoxyphene-associated deaths reached a peak in 1977, then declined by 22.2% from 1977 to 1978 and by 33.3% from 1978 to 1979. This decline occurred despite increased interest in propoxyphene misuse and the existence of improved analytical methods for the detection of propoxyphene. The decline is greater than can be accounted for by the decline in propoxyphene prescribing.

The most common manner of death was suicide, accounting for 44.1% of the total cases and 54% of the drug-caused deaths; it can be safely assumed that the suicides were underreported. A large majority (88.6%) of the suicides involving propoxyphene were multiple-drug intoxications, including alcohol. Propoxyphene alone was noted in 17.3% of the 820 suicides.

The vast majority (94%) of cases involved persons between the ages of 20 and 40. There were very few instances of pediatric, adolescent, or older adult deaths associated with propoxyphene in this study. The distribution of males to females, racial origin and occupation approximated that of the U.S. population; however, the majority were white, blue-collar workers. Nearly three fourths (71%) of the deceased were discovered at home or at the residence of a friend.

The survey population showed a marked tendency toward nonspecific, minor, common, painful ailments; however, no single ailment predominated. Documentation existed to show that 44.6% of the deceased had recent ill health.

Approximately 59% of the entire survey population had documented emotional disturbances or drug-abuse problems. The most common condition among this population was manifest in unusual despondency at or near the time of death. Almost 10% of these patients had previously attempted suicide, and 12% of them were undergoing psychiatric treatment at the time of death.

This study provides no evidence to support the view that the deceased were part of the street-drug-abuse population. A history of heroin abuse appeared in less than 5% of the cases. Even fewer (1.8%) had been known to have abused propoxyphene before their deaths. But 18% of the population had been known to "self-medicate," using multiple drugs without appropriate medical supervision.

Propoxyphene alone was involved in 18.1% of the 1859 cases. The remaining 81.9% involved propoxyphene and at least one other drug, including alcohol. The combination of propoxyphene and alcohol alone was detected in 17.5% of the cases. Most of the blood alcohol concentrations noted were significant; 48% were in the range of 0.10 to 0.25%, strongly suggesting heavy, habitual alcohol usage. Similarly, in most of the multiple drug

cases the individual drugs, other than propoxyphene and alcohol, were present in toxic and often lethal concentrations.

Approximately 55% of the drug deaths were known to have occurred within 10 h after ingestion of the drug or the time when the deceased was last seen alive. Overnight deaths (9 h) accounted for 16% of the cases. Only 10% of the total deceased population died within 1 h of drug ingestion.

Almost three fourths of the deceased had blood propoxyphene concentrations of 5 μg/mL or less. Of the cases in which only propoxyphene was involved, 90.6% of the blood concentrations were at or below 5 μg/mL.

There were no cases in which norpropoxyphene alone was found in blood after the ingestion of propoxyphene only, nor were there any cases in the survey that demonstrated a causative norpropoxyphene toxicity in an accidental fatality.

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References

[1] Cravey, R. H., Shaw, R. F., and Nakamura, G. R., "Incidence of Propoxyphene Poisoning: A Report of Fatal Cases," *Journal of Forensic Sciences*, Vol. 19, No. 1, Jan. 1974, pp. 72-80.

[2] Chambers, D. C., Moffett, A. D., and Cuskey, W. R., "Five Patterns of Darvon Abuse," *The International Journal of Addiction*, Vol. 6, 1971, pp. 173-189.

[3] Sturner, W. Q. and Garriott, J. C., "Deaths Involving Propoxyphene. A Study of 41 Cases over a Two-Year Period," *Journal of the American Medical Association*, Vol. 233, 1973, pp. 1125-1130.

[4] Young, D. J., "Propoxyphene Suicides," *Archives of Internal Medicine*, Vol. 129, 1972, pp. 62-66.

[5] McBay, A. J. and Hudson, P., "Letter: Propoxyphene Overdose Deaths," *Journal of the American Medical Association*, Vol. 233, 1975, p. 1257.

[6] Baselt, R. C., Wright, J. A., Turner, J. E., and Cravey, R. H., "Propoxyphene and Norpropoxyphene Tissue Concentrations in Fatalities Associated with Propoxyphene Hydrochloride and Propoxyphene Napsylate," *Archives of Toxicology*, Vol. 34, 1975, pp. 145-152.

[7] McBay, A. J. and Hudson, P., "Drug Deaths in North Carolina: A Brief Survey of Deaths Attributed to Drugs in North Carolina, 1973," *North Carolina Medical Journal*, Vol. 35, 1974, pp. 542-544.

[8] 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.

[9] Hudson, P., Barringer, M. A. B., and McBay, A. J., "Fatal Poisoning with Propoxyphene: Reports from 100 Consecutive Cases," *Southern Medical Journal*, Vol. 70, 1977, pp. 938-942.

[10] Cimbura, G., "Propoxyphene-Associated Fatalities in Ontario, Incidence and Forensic Toxicological Aspects," *Canadian Society of Forensic Science Journal*, Vol. 12, 1979, pp. 173-175.

[11] Poklis, A. and Gantner, G. E., "Deaths Attributed to Drugs in St. Louis City and County. A Brief Survey 1977-1978," *Missouri Medicine*, Nov. 1979, pp. 588-590.

[12] Eli Lilly & Co., "Darvon® and Darvon-N®: Third Quarterly Report," Food and Drug Administration, Washington, D.C., 14 May 1980, pp. 7-8.

[13] Massey, J. T., "Suicide in the United States," National Center for Health Statistics, Department of Health, Education and Welfare Series 20, No. 5, Aug. 1967, pp. 1-34.

[14] McBay, A. J., Turk, R. F., Corbett, B. W., and Hudson, P., "Determination of Propoxyphene in Biological Materials," *Journal of Forensic Sciences*, Vol. 19, No. 1, Jan. 1974, pp. 81-89.

[15] Amsterdam, E., "Depression of Myocardial Contractile Function by Propoxyphene and Norpropoxyphene," *Journal of Cardiovascular Pharmacology*, Vol. 3, 1981, pp. 129-138.

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