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Forensic Toxicology of Some Deaths Associated with the Combined Use of Propoxyphene and Acetaminophen (Paracetamol)

For many years the most commonly encountered mild analgesic in cases of poisoning in the United Kingdom and particularly in London was aspirin. Often aspirin was formulated with phenacetin and codeine and sometimes with caffeine. Chronic use of phenacetin was found to cause renal damage, but, though acetaminophen is a metabolite of phenacetin, there is no evidence that it does harm to the kidney. Acetaminophen is itself a mild analgesic that has gained favor as an alternative to both phenacetin and aspirin since it does not cause gastric ulceration and hemorrhage when taken orally.

Tablets containing aspirin and codeine, and acetaminophen and codeine, are available as over-the-counter remedies, but a proprietary formulation of acetaminophen with dextropropoxyphene (Distalgesic® in the United Kingdom) is widely prescribed as an analgesic preparation. It is often available and used by those attempting suicide.

The first cases of poisoning associated with acetaminophen that were confirmed by analysis of blood or other body fluids were seen during 1972 at the London Hospital Medical College; though acetaminophen only was present in some instances, it was more usual to find it in combination with aspirin or, more often, propoxyphene, especially when the overdose proved fatal.

This paper presents toxicological data for autopsy cases occurring during 1972 through 1976 in which death was associated with ingestion of Distalgesic tablets alone or in combination with alcohol or other drugs. Each tablet contains 32.5 mg dextropropoxyphene hydrochloride and 325 mg paracetamol (acetaminophen). Data for three deaths attributed to acetaminophen poisoning and three related to propoxyphene overdosage are included for comparative purposes. None of the case histories included any reference to the persistent nonmedical use of drugs or of drug dependence, and natural disease was not considered a contributory factor in relation to the cause of death in any of the cases discussed.

Experimental Methods

Preliminary qualitative analysis was carried out by using portions of stomach content and urine to ascertain the nature of the drugs present [*1*]. Except where otherwise noted, the autopsy blood samples were collected from peripheral vessels.

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Determination of Acetaminophen

One millilitre of specimen acidified to pH 3.0 with hydrochloric acid was extracted with 50 ml diethyl ether. The solvent extract was filtered through Whatman No. 4l filter paper and after the addition of 100-μg *p*-toluic acid (as external standard) was evaporated to dryness over a hot water bath. After drying overnight in a desiccator the residue was dissolved in 50-μl dried acetone and 50-μl N,O-bistrimethylsilylacetamide was added; the solution was heated at 60°C for 30 min. About 3-μl portions of the silylated extract were used for gas chromatography. Aqueous standard solutions containing acetaminophen were extracted in parallel with the biological samples. The ratio of the areas of the peaks for the trimethylsilyl (TMS) derivatives of acetaminophen to 100-μg *p*-toluic acid showed a linear relation to the concentration of acetaminophen over the range 10 to 200 μg.

Gas chromatography was performed with a Hewlett-Packard 5750 gas chromatograph fitted with a flame ionization detector and a 1.8-m glass column of 3.5-mm internal diameter, packed with 3.8% W-98 on 80-100 mesh AW-DMCS Chromosorb W. The oven temperature was maintained at 160°C with the injection port at 250°C and the detector at 400°C. Nitrogen was the carrier gas at a flow rate of 40 ml/min. Under these conditions the retention time of the TMS derivative of *p*-toluic acid was 3 min and of acetaminophen was 8 min.

Determination of Propoxyphene and Norpropoxyphene

The pH value of 5 ml of blood or urine (or 1 ml of bile or stomach content with 4 ml of water) was adjusted to 12 by the addition of 2 ml 1*N* sodium hydroxide solution, and the mixture was allowed to stand at ambient temperature for 1 h to allow the rearrangement of norpropoxyphene to norpropoxyphene amide to proceed to completion. The samples were extracted with 50 ml butyl chloride and the solvent was filtered through Whatman No. 41 filter paper. Dibenzepin (100 μg) was added to the solvent extract before evaporation to dryness over a boiling water bath. The residue was reconstituted in 50 μl ethanol and aliquots of about 3 μl were used for gas chromatography. Aqueous standard solutions of dextropropoxyphene hydrochloride and of norpropoxyphene maleate were prepared from pure samples of the salts provided by Eli Lilly and Co. Portions of the standard solutions were treated and extracted in parallel with the biological samples. The ratios of the areas of the gas chromatographic peaks for propoxyphene and norpropoxyphene to 100 μg dibenzepin were linear over the range 25 to 500 μg.

The gas chromatograph was an F & M Biomedical 400 fitted with a flame ionization detector. The 1.2-m glass column, 3-mm internal diameter, was packed with 3.8% W-98 on 80-100 mesh Diatoport S and maintained at 200°C. The injection port and the detector temperatures were held at 250°C. The carrier gas was nitrogen at a flow rate of 40 ml/min. Under these conditions the retention times were propoxyphene, 4.6 min; dibenzepin, 10 min; and norpropoxyphene amide, 13.6 min.

Gas Chromatographic Determination of Alcohol and Other Drugs

Alcohol was determined using *n*-propanol as an internal standard following the method of Curry et al [*2*].

Barbiturate was assayed in chloroform extracts using barbital as an internal standard. Gas chromatographic conditions were as described for acetaminophen except that the oven temperature was raised to 195°C. The retention times were barbital, 1.2 min; amobarbital, 2.8 min; pentobarbital, 3.1 min; and secobarbital, 3.6 min.

Salicylic acid was determined, as the TMS derivative, on the column and with the same conditions and external standard as for acetaminophen; the retention time was 4 min.

Dihydrocodeine was extracted into chloroform under alkaline conditions and assayed using trihexyphenidyl (benzhexol) as external standard. The gas chromatographic conditions were the same as for propoxyphene. The retention times were trihexyphenidyl, 9 min and dihydrocodeine, 14 min.

Chloroquine was assayed as described previously [*3*].

Chlorpromazine was extracted into chloroform under alkaline conditions and was determined in the extracts with codeine used as external standard; the gas chromatographic conditions were the same as for acetaminophen except that the oven temperature was raised to 245°C. The retention times were codeine, 5.5 min and chlorpromazine, 7.5 min.

Nitrazepam was determined by the method of Beharrell et al [*4*] but with a flame ionization detector.

Results

Table 1 shows the distribution of acetaminophen, propoxyphene, and norpropoxyphene in four cases in which the autopsy findings were those of hypoxia and the cause of death was attributed to poisoning on the basis of the analytical data. In each of these cases the time interval between ingestion of tablets and death was about 9 h, which accords with the findings in the recent survey by Finkle et al [*5*].

TABLE 1—*Analytical data for autopsy specimens from cases of fatal poisoning by acetaminophen and propoxyphene. Each victim was found dead with circumstantial evidence of having taken Distalgesic tablets about 9 h earlier. The autopsy findings were those associated with hypoxia.*

Case	Sex/Age	Sample	Acetaminophen, μg/ml or μg/g	Propoxyphene, μg/ml or μg/g	Norpropoxyphene, μg/ml
1	f/17	blood	294	1.8	1.1
		liver blood	337	6.1	9.1
		bile	413	100	15
		urine	298	13.8	2.2
		total stomach content, mg	(330)	(84)	...
2	m/21	blood	65	0.9	ND[a]
		liver blood	141	2.2	1.8
		bile	260	41	46
		urine	140	24	12.6
		total stomach content, mg	(1.7)	(8.7)	ND[a]
3	f/24	blood	193	1.5	1.5
		bile	18	4.5	15.4
		total stomach content, mg	(350)	(48)	...
4	f/69	blood	615	1.2	...
		liver	77	63	...
		lung	518	0.9	...[b]
		spleen	780	40	...
		kidney	657	4.3	...
		brain	247	1.6	...

[a]ND = not detected.
[b]Not determined.

Results for two contrasting cases are shown in Table 2. Case 1, a 66-year-old man, was found collapsed and unrousable 2 h after he had been seen alive and had written a note indicating that he had taken 25 Distalgesic tablets. Case 2 was a 36-year-old female who took an overdose of Distalgesic tablets and suffered a grand mal seizure and cardiorespiratory failure. She was resuscitated by an ambulance crew and was admitted unconscious to a hospital, where she died three days later.

TABLE 2—*Fatal poisonings by acetaminophen and propoxyphene; results for one victim who survived for 2 h and one who lived for three days in hospital after ingestion of the drug.*

Case	Sex/Age	Sample	Acetaminophen, μg/ml or μg/g	Propoxyphene, μg/ml or μg/g	Norpropoxyphene, μg/ml or μg/g
1	m/66	blood	83	8.6	...[a]
		bile	38	102	...[a]
		total stomach content, mg	(70)	(105)	...[a]
2	f/36	blood (antemortem)	41	29	ND[b]
		urine (antemortem)	13	4.6	16
		blood (postmortem)	<1	<0.3	<0.3
		bile	47	49	445
		liver	7	1.3	1.8
		lungs	...	1.6	0.6
		kidneys	...	1.3	0.3
		spleen	...	1.5	0.5
		brain	ND	1.3	<0.3

[a] Not determined.
[b] ND = not detected.

Results for cases in which alcohol had been consumed in addition to Distalgesic tablets are shown in Table 3. Data for some "drug cocktail" deaths in which significant concentrations of acetaminophen and propoxyphene were found are included in Table 4.

Table 5 gives the results for cases in which acetaminophen only was found. Table 6 shows results for propoxyphene-related deaths in which acetaminophen was not present.

TABLE 3—*Analytical results for autopsy specimens of victims found dead 7 to 10 h after taking acetaminophen and propoxyphene following consumption of alcohol.*

Case	Sex/Age	Sample	Acetaminophen, μg/ml	Propoxyphene, μg/ml	Norpropoxyphene, μg/ml	Alcohol, mg/100 ml
1	m/20	blood (heart)	140	3.1	0.6	110
		thoracic cavity fluid	195	9.1	1.0	...
		urine	190	5.6	4.6	173
2	f/23	blood	356	3.2	...[a]	159
		urine	191	1.0	...	206
		total stomach content, g	(1.8)	(0.8)	...	...
3	f/26	blood	366	3.0	0.5	174
		liver blood	249	25	8	106
		bile	176	26	123	...
		total stomach content, mg	(40)	(45)	...	...
4	f/33	blood	202	2.0	1.4	119
		liver blood	223	14	4.2	85
		bile	680	125	112	...
		urine	51	3.2	2.8	193
		total stomach content, mg	(155)	(6.6)	...	...
5[b]	m/50	blood	16	5.0	0.5	245
		liver blood	42	9	...	197
		bile	...	...	...	268
		urine	9.0	2.0	0.2	368
		total stomach content, mg	(9.3)	(1.4)	...	...

[a] Not determined.
[b] This victim had access to various drugs and may not have taken Distalgesic.

TABLE 4—*Drug "cocktail" deaths: analytical results for cases in which acetaminophen and propoxyphene were found in combination with other drugs.*

Case	Sex/Age	Sample	Acetaminophen, μg/ml or μg/g	Propoxyphene, μg/ml or μg/g	Norpropoxyphene, μg/ml	Salicylic Acid, μg/ml or μg/g	Alcohol, mg/100 ml	Other, μg/ml or μg/g
1	f/14	blood	101	8.3	4.9	34	ND[a]	...
		liver blood	243	20.3	4.9	19	ND	...
		bile	...	96.4	18.2	...	ND	...
		urine	163	4.7	9.9	53	ND	...
		total stomach content, mg	(255)	(380)	(0.27)	(45)	ND	...
2	f/18	blood	3.0	2.7	...	630	ND	dihydrocodeine, 1.6
		bile	38	96	...[b]	6570	ND	dihydrocodeine, 16
		urine	2.3	0.8	...	2890	ND	dihydrocodeine, 79
		total stomach content, mg	(2)	(16)	...	(8)	ND	dihydrocodeine, (0.7)
3	f/58	blood	625	1.0	...	1030	ND	chloroquine, 56
		total stomach content, mg	(810)	(162)	...[b]	(2.2)	ND	chloroquine, (300)
		liver	0.5	4.9	...	295	ND	chloroquine, 770
		lungs	0.1	2.1;1.1	...	223;200	ND	chloroquine, 290;350
		spleen	0.1	2.7	...	360	ND	chloroquine, 1300
		kidneys	0.1	0.8	...	838;708	ND	chloroquine, 420;250
		brain	...	1.0	...	...	ND	chloroquine, 80
4	f/67	blood	20	1.0	...[b]	56	123	pentobarbital, 19
		liver blood	132	4.0	...	983	...	pentobarbital, 83
		urine	...	0.5	0.5	...	10	pentobarbital, 2.0
		total stomach content, mg	(200)	(237)	...	(7000)	...	pentobarbital, (1400)
5	f/40	blood	388	3.5	0.1	ND	126	chlorpromazine, 6.8
		liver blood	878	44	10	ND	79	chlorpromazine, 34
		bile	1325	245	225	ND	...	chlorpromazine, 97
		urine	179	3.0	5.4	ND	154	chlorpromazine, 3.0
		total stomach content, mg	(198)	(174)	ND	ND	...	chlorpromazine, (72)
6	m/58	blood	251	0.8	ND	ND	209	nitrazepam, 0.7
		liver blood	287	15	4.0	ND	...	nitrazepam, 0.7
		bile	131	13	15	ND	...	nitrazepam, 2.0
		urine	180	6	ND	ND	232	nitrazepam, 1.3

[a] ND = not detected.
[b] not determined.

TABLE 5—*Three acetaminophen fatalities: analytical data for autopsy specimens.*

Case	Sex/Age	Sample	Acetaminophen, μg/ml or μg/g	History
1	f/23	blood	200	schizophrenic; had taken drug overdoses before and her husband kept her supply of prescribed drugs. Died after deliberate ingestion of ≈60 tablets (30 g acetaminophen).
		urine	620	
		total stomach content, g	(3.3)	
2	f/55	blood	387	admitted unconscious to hospital after overdose. Died ≈30 h later with grossly abnormal serum glutamic oxalacetic transaminase level. Gastric lavage had been performed.
		liver blood	475	
		bile	900	
		total stomach content, mg	(105)	
		liver	385	
		lungs		
		left	597	
		right	426	
		kidneys	93;188	
		spleen	498	
3	m/62	blood	160	found dead in bed. Had been treated for a nervous breakdown and had made many attempts at suicide.
		liver blood	200	
		bile	180	
		urine	180	
		total stomach content, mg	(300)	

TABLE 6—*Results for three propoxyphene-linked fatalities in which acetaminophen was not found.*

Case	Sex/Age	Sample	Propoxyphene, μg/ml	Norpropoxyphene, μg/ml	Other
1	f/44	blood	2.5	2.6	...
		liver blood	13	15.1	...
		bile	107	900	...
		urine	30	209	...
		total stomach content, mg	(0.5)	(0.025)	...
2	m/38	blood	3.2	3.8	alcohol, 182 mg/ 100 ml
		liver blood	144	16.7	...
		bile	115	155	...
		urine	34	28	alcohol, 265 mg/100 ml
		total stomach content, mg	(56)	(0.084)	...
3	m/19	blood	9.1	1.1	amobarbital, 6.0 μg/ml secobarbital, 4.0 μg/ml
		liver blood	106	42	amobarbital, 8.0 μg/ml secobarbital, 5.0 μg/ml
		bile	65	213	...
		urine	35	13.5	amobarbital, 3.0 μg/ml secobarbital, 2.0 μg/ml
		total stomach content, mg	(0.9)	(0.3)	amobarbital, 5.5 mg secobarbital, 6.5 mg

Discussion

Acetaminophen Concentrations in Autopsy Specimens

The autopsy blood concentrations of acetaminophen found in the cases included in Tables 1 to 5, except for Case 5 in Table 3 and Cases 2 and 4 in Table 4, are all well in excess of what might be termed the "therapeutic range" and most are comparable with plasma concentrations in clinical overdose cases.

Thus, following a dose of 1 g acetaminophen, the peak plasma concentration is achieved after 45 min and is in the range of 5 to 25 μg/ml. In a recent study Lowenthal et al [*6*] observed peak plasma concentrations of 6 to 7 μg/ml 0.5 to 1 h after the administration of 1 g acetaminophen per 1.73 m^2 body surface area; after 7 h the plasma concentration had fallen to 1 μg/ml. The mean biological half-life of 142 min was within the range of 90 to 180 min noted in other studies. The same dose of acetaminophen given to anephric patients results in peak plasma concentrations of about 10 μg/ml after 1 h, falling to about 2 μg/ml at 7 h. The mean biological half-life of acetaminophen in the anephric patients was similar to that for healthy subjects though drug metabolites accumulated in the plasma of the former group.

Kendal et al [*7*] refer to plasma concentrations of acetaminophen of 400 to 500 μg/ml in overdose cases, and their data accord with ours for clinical blood samples in showing that plasma concentrations are about 20% higher than for whole blood. The plasma half-life of acetaminophen is increased when the drug is taken in overdose; hepatic damage is probable if the half-life exceeds 4 h and if the plasma concentration is in excess of 300 μg/ml 4 h after ingestion. The highest serum concentration for a nonfatal clinical case in our records is 390 μg/ml.

The results for the acetaminophen-only autopsy cases (Table 5) show that the drug is widely distributed; its secretion in the bile may be significant in relation to hepatic necrosis, particularly if the drug exerts a direct effect on the liver cells. The data refer to the concentrations of acetaminophen per se and do not include the metabolites. The highest autopsy blood concentration of acetaminophen in our records is 810 μg/ml for an elderly lady of 70 years found collapsed and with bronchopneumonia.

Propoxyphene in Autopsy Specimens

Sturner and Garriott [*8*] found autopsy blood propoxyphene concentrations of 1.2 to 11 μg/ml and liver concentrations of 2.1 to 288 μg/g for eight fatalities in which no other drug was found. In eleven cases in which alcohol was significant, the blood concentrations of propoxyphene ranged from 1.2 to 25 μg/ml (liver, 10 to 136 μg/g) and the highest blood concentration in a death ascribed to natural causes was 3.8 μg/ml. The authors also found that the concentration of propoxyphene in the liver and the kidney usually exceeded that of the blood, that the lung concentration often exceeded that of the liver, and that more than 2 μg/ml blood in a nontolerant individual was consistent with intoxication.

A later study by Cravey et al [*9*] reported autopsy blood propoxyphene concentrations in the range of 1.0 to 60 μg/ml (23 cases) and liver concentrations ranging from 5 to 5500 μg/g (73 cases) where no other drugs contributed to death. The liver concentration of propoxyphene varied from 2 to 384 μg/g in cases containing significant concentrations of alcohol in the blood.

Baselt et al [*10*] referred to four fatalities having propoxyphene concentrations of 8 to 14 μg/ml blood and 30 to 272 μg/g liver at autopsy. The same four cases appear to be included in another paper by Baselt et al [*11*] in which the propoxyphene concentrations in the autopsy specimens were in the range of 0.4 to 8.3 μg/ml blood and 8 to 69 μg/g liver together with norpropoxyphene concentrations of 0.8 to 13.8 μg/ml blood and 16.6 to 186

μg/g liver. Fatalities in which significant concentrations of alcohol were present also were reported to contain propoxyphene, 0.4 to 2.4 μg/ml blood and 2.3 to 118 μg/g liver, and norpropoxyphene, 2.4 to 8.3 μg/ml blood and 19.3 to 208 μg/g liver.

Other cases reported in the literature contain a variety of other drugs or refer to subjects known or suspected to be dependent on the drug. In a recent survey, McBay [*12*] concluded that an autopsy blood propoxyphene concentration of 1 μg/ml is consistent with death caused by the drug though, unfortunately, most of his cases also contained other drugs. Finkle et al [*5*] concluded that most "fatal blood concentrations" were in the range of 1 to 4 μg/ml.

Only one death attributed to propoxyphene alone has been encountered during the five-year period of this study (Table 6, Case 1). The blood concentration of the unchanged drug is within the range of reported cases and about equal to that of norpropoxyphene, the major metabolite in man [*13*]. Our case compares with the two cases given by McBay [*12*] in which no other drug or alcohol was involved and in which the blood concentrations of the drug and its metabolites were found to be similar.

Welling et al [*14*] studied the influence of diet and fluid on plasma concentrations of propoxyphene and norpropoxyphene in volunteers given 130 mg dextropropoxyphene hydrochloride by mouth. Diet influenced the rate of absorption and the time at which peak plasma concentrations of propoxyphene (about 0.2 μg/ml) were achieved; the plasma concentrations of norpropoxyphene correlated with those of the unchanged drug after 2 h and at 8 h exceeded those of propoxyphene by a factor of about 3.5. The plasma half-life of propoxyphene is about 3 h, whereas for norpropoxyphene it is much longer: 16.2 h [*14*, *15*], at least for doses of dextropropoxyphene in the therapeutic range. Peak propoxyphene plasma concentrations of 0.85 μg/ml have been recorded when the drug is given on a chronic basis [*16*]. While the rates of metabolism and excretion of propoxyphene taken in toxic doses may vary, it seems probable that the proportions of drug and metabolite may provide a more suitable basis for the interpretation of autopsy data than the drug concentrations per se.

One case involving propoxyphene and alcohol but no other drug (Table 6, Case 2) also showed comparable concentrations of the drug and its metabolite in the blood at autopsy. In this and in Case 1 of Table 6, the relatively higher concentrations of propoxyphene and norpropoxyphene in the bile may reflect the biliary secretion both of the drug and its metabolite, which is, of course, formed in the liver. Norpropoxyphene may also be secreted into the gastric juice since it is often found in the stomach content at autopsy. The amount found may perhaps be related to the survival time after ingestion of the drug.

The propoxyphene-Tuinal® fatality (Table 6, Case 3) appears to have resulted from respiratory failure after the administration of therapeutic amounts of each drug; the high biliary concentration of norpropoxyphene and the amount in the stomach content probably reflect previous dosage of propoxyphene.

Acetaminophen and Propoxyphene in Combination

The data in Table 1 relate to four cases in which Distalgesic was thought to have been the only drug taken; there was no evidence at the scene to suggest that separate dose forms of acetaminophen and dextropropoxyphene were available or could have been taken. The relative amounts of each drug remaining in the stomach content of each case shows that the drugs are absorbed at different rates. Each Distalgesic tablet contains 325 mg acetaminophen and 32.5 mg dextropropoxyphene hydrochloride (equivalent to 29 mg of the base). The blood concentrations of acetaminophen are well in excess of peak plasma levels after single therapeutic doses of 1 g and are in the toxic, though not necessarily liver-damaging, range discussed by Kendal et al [*7*]. The propoxyphene blood concentrations are towards the lower end of the range found when only that drug is implicated, but in Cases 1 and 2

they exceed the concentrations of the metabolite. Whether this is due to the hepatotoxic effects of acetaminophen causing interference with the microsomal enzymes responsible for *N*-demethylation or whether the time factor is significant is a matter for conjecture. The propoxyphene distribution observed in Case 4 of Table 1 is strange though possibly a consequence of the liver damage, which is almost inevitably associated with such a high blood concentration of acetaminophen.

In contrast with the cases in Table 1, those in Table 2 collapsed within a much shorter time of ingesting the drug and this is reflected by the analytical data. Thus, Case 1 of Table 2 shows a proportionally higher blood concentration of propoxyphene than acetaminophen, contrasting markedly with the previous cases.

Similarly, the propoxyphene concentrations in the antemortem blood in Case 2 of Table 2 is not only proportionately high in relation to the acetaminophen but was also probably sufficient to cause respiratory depression and hypoxic seizures. The persistence of the norpropoxyphene in the bile until death is less surprising if liver function was maintained even though norpropoxyphene was not detectable in the antemortem blood. The time at which the antemortem specimens were taken was not known.

Alcohol Taken with Acetaminophen and Propoxyphene

Cases 1 through 4 of Table 3 were all thought to have taken Distalgesic tablets, but Case 5 may have taken the drugs separately. The acetaminophen blood concentrations in Cases 1 through 4 are of the same order as the data in Table 1, whereas the blood propoxyphene concentrations are slightly higher and exceed those of norpropoxyphene. Each of the case histories included alcohol consumption before rather than with the tablets. Alcohol present in the stomach may have facilitated drug absorption, particularly of propoxyphene.

The biliary concentrations of norpropoxyphene, particularly in Cases 3 and 4, are notable, particularly since 7 to 10 h elapsed between ingestion of Distalgesic and death and the metabolite blood level is less than that of propoxyphene.

Acetaminophen and Propoxyphene Combined with Other Drugs

The available data for six cases are shown in Table 4; the common feature is the probable inclusion of Distalgesic tablets in the "cocktail" of drugs taken and the presence of significant concentrations of propoxyphene at autopsy. The relationship and distribution of propoxyphene and its metabolite compare with the cases already discussed. The acetaminophen concentrations found in Cases 2 and 4 do not appear to be excessive.

Cases 1, 5, and 6 show toxicological results consistent with death resulting from poisoning by acetaminophen and propoxyphene, and in the latter two cases alcohol must have been contributory. The salicylic acid concentrations in Case 1 are consistent with therapeutic dosage. It may be relevant to note that in therapeutic doses neither the plasma concentration of propoxyphene nor that of salicylate was influenced by the simultaneous administration of the two drugs [*17*].

Case 2 shows blood concentrations of propoxyphene, salicylic acid, and dihydrocodeine, each of which in the absence of the other substances would be sufficient to have caused death; comparatively small amounts of the drugs remained in the stomach content, and the biliary concentration of each drug exceeds that of the blood.

Cases 3 and 4 are clear examples of massive overdoses from the quantities of drugs found in the stomach content. Death in Case 3 could have resulted from poisoning by acetaminophen, propoxyphene, salicylic acid, or chloroquine; the deceased was chronically depressed and had taken a drug overdose in the past. In Case 4, death probably resulted from the combined depressant effects on the central nervous system of propoxyphene, alcohol, and pentobarbital. Though a large quantity of salicylate was present in the stomach content,

the peripheral blood level was not excessive. The blood/urine ratio for the alcohol concentration implies that alcohol was recently ingested and perhaps used to aid the swallowing of the other drugs.

References

[1] Robinson, A. E. and Holder, A. T., "Chemical Evaluation of 'Drug Cocktails' in Autopsy Specimens," *Journal of Chromatographic Science*, Vol. 12, May 1974, pp. 281–284.

[2] Curry, A. S., Walker, G. W., and Simpson, G. S., "Determination of Ethanol in Blood by Gas Chromatography," *Analyst*, Vol. 91, 1966, pp. 742–743.

[3] Robinson, A. E., Coffer, A. I., and Camps, F. E., "The Distribution of Chloroquine in Man After Fatal Poisoning," *Journal of Pharmacy and Pharmacology*, Vol. 22, No. 9, Sept. 1970, 700–703.

[4] Beharrell, G. P., Hailey, D. M., and McLaurin, M. K., "Determination of Nitrazepam (Mogadon) in Plasma by Electron Capture Gas-Liquid Chromatography," *Journal of Chromatography*, Vol. 70, 1972, pp. 45–52.

[5] 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.

[6] Lowenthal, D. T., Øie, S., Van Stone, J. C., Briggs, W. A., and Levy, G., "Pharmacokinetics of Acetaminophen Elimination by Anephric Patients," *Journal of Pharmacology and Experimental Therapeutics*, Vol. 196, No. 3, 1976, pp. 570–578.

[7] Kendal, S. E., Lloyd-Jones, G., and Smith, C. F., "The Development of a Blood Paracetamol Estimation Kit," *Journal of International Medical Research*, Vol. 4, Supplement (4), 1976, March 1973, pp. 1125–1130.

[8] 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. 223, No. 10, pp. 1125–1130.

[9] 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.

[10] Baselt, R. C., Wright, J. A., and Cravey, R. H., "Therapeutic and Toxic Concentrations of More Than 100 Toxicologically Significant Drugs in Blood, Plasma, or Serum: A Tabulation," *Clinical Chemistry*, Vol. 21, No. 1, 1975, pp. 44–62.

[11] 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," *Archiv fur Toxikologie*, Vol. 34, 1975, pp. 145–152.

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

[13] McMahon, R. E., Ridolfo, A. S., Culp, H. W., Wolen, R. L., and Marshall, F. J., "The Fate of Radiocarbon-Labelled Propoxyphene in Rat, Dog, and Human," *Toxicology and Applied Pharmacology*, Vol. 19, 1971, pp. 427–444.

[14] Welling, P. G., Lyons, L. L., Tse, F. L. S., and Craig, W. A., "Propoxyphene and Norpropoxyphene: Influence of Diet and Fluid on Plasma Levels," *Clinical Pharmacology and Therapeutics*, Vol. 19, No. 5, Part 1, 1976, pp. 559–565.

[15] Verebely, K. and Inturrisi, C. E., "Disposition of Propoxyphene and Norpropoxyphene in Man after a Single Oral Dose," *Clinical Pharmacology and Therapeutics*, Vol. 15, No. 3, March, 1974, pp. 302–308.

[16] Verebely, K. and Inturrisi, C. E., "The Simultaneous Determination of Propoxyphene and Norpropoxyphene in Human Biofluids Using Gas-Liquid Chromatography," *Journal of Chromatography*, Vol. 75, 1973, pp. 195–205.

[17] Nash, J. F., Scholz, N. E., and Maxwell, S. B., "A Study of Propoxyphene and Salicylate Concentrations in Human Plasma Following Administration of Propoxyphene Napsylate and Aspirin," *Toxicology and Applied Pharmacology*, Vol. 19, 1971, pp. 537–545.

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