

Propoxyphene and Norpropoxyphene Concentrations in Blood and Tissues in Cases of Fatal Overdose

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Propoxyphene and its major metabolite, norpropoxyphene, have been quantitated in tissue specimens obtained from autopsies of people suspected of dying from propoxyphene overdose. Gas-chromatographic determination of both propoxyphene and norpropoxyphene is essential because the blood concentration of the parent drug should be about 1.0 mg/liter or greater to attribute a death to the drug. The metabolite concentration in blood may help to establish when the drug was ingested. Concentrations in the blood after high oral therapeutic doses are about 0.3 mg of propoxyphene per liter, and norpropoxyphene concentrations may be as high as 3 mg/liter. Methods of determining propoxyphene are discussed.

Additional Keyphrases: *drug abuse • drug monitoring • measurement of metabolites • toxicology • ultraviolet spectrophotometry • gas chromatography*

Propoxyphene, a popular prescription analgesic, is most commonly sold as Darvon but also is available under a number of other names (1). Recently, attention has been focused on this drug because of the increased number of deaths attributed to it (2). In North Carolina, if one excludes alcohol, propoxyphene caused more deaths than any other drug in 1975.

Propoxyphene is not easily quantitated in blood. A survey of the results of analyses of propoxyphene-containing serum samples by a large number of clinical laboratories revealed that more than one-third of the laboratories did not perform such an analysis, about one-quarter identified the drug but did not quantitate it, and only about one-eighth of the laboratories reported results that were within 30% of the target value (3).

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Methods for determination of this drug have been inefficient because the drug absorbs ultraviolet light poorly, and because of molecular changes that occur on acidic or alkaline hydrolysis and heating. Advantage has been taken of the increase in absorbance produced by acidic hydrolysis in one method of determination (4). The earlier methods are reviewed in this same reference. A fluorometric method has appeared since that review (5). The most recent work involves gas chromatography, which in some cases is combined with mass spectrometry (6-8).

Two methods of determination will be discussed in this paper: in one ultraviolet spectrophotometry is used (4), in the other gas chromatography. Propoxyphene and two metabolites, norpropoxyphene and cyclic dinorpropoxyphene, are present in blood, all in relatively small amounts. It is desirable to measure the concentrations of propoxyphene and norpropoxyphene. The ultraviolet method (4), when used alone, does not allow one to distinguish propoxyphene from norpropoxyphene.

It is important to determine both the concentration of the drug and of its major metabolite to decide whether there is enough drug present to account for death and possibly to serve as an indication of when the drug was taken. In one study (6), about 75% of the drug was present as propoxyphene and 25% as norpropoxyphene 1 h after its ingestion, in 2 h the amounts were equal, and in 6 h 25% was present as propoxyphene and 75% as norpropoxyphene. The biological half-life of propoxyphene is about 12 h, of norpropoxyphene about 36 h (7). Errors in estimation may be expected when the person may have residual norpropoxyphene present as a result of continued use and then takes an overdose. For death to be attributed to propoxyphene it is es-

Table 1. Drug Concentrations in Blood after Fatalities Attributed to Propoxyphene

Case	Age, sex	Propoxyphene	Norpropoxyphene mg/liter	Salicylate	Ethanol, g/liter	Manner of death	Alleged propoxyphene
1	47M	4.9	1.4	—	1.1	suicide	Darvon
2	26F	4.9	2.3	—	1.1	suicide	Darvon-N
3	19M	4.1	5.9	0	0.4	accident	Darvon-N
4	53M	2.6	2.5	—	0	unknown	Darvon
5	55F	1.1	5.1	80	0	accident	Darvon
6	22F	3.5	4.0	—	0	suicide	Darvocet
7	36F	0.8	2.0	70	0	unknown	Darvon
8	42M	0.8	2.3	—	2.0	accident	Darvon
9	32F	3.0	3.0	170	0	suicide	Darvon
10	36F	21.0	5.5	100	0	suicide	Darvon
11	39F	6.0	7.0	280	2.1	suicide	—
12	22M	0.8	2.0	—	3.1	accident	—
13	44M	0.6	7.0	60	0	accident	Darvon
14	50M	2.0	0.8	0	0	accident	Darvon
15	24M	2.0	2.0	0	1.8	suicide	Darvocet

Notes: Specimens in cases 1–6 were analyzed by analysts at Eli Lilly & Co.

Case 2: Diazepam, 0.7 mg/liter; Case 5: Phenobarbital, 9 mg/liter; Case 7: Codeine, 0.7 mg/liter; Case 13: Hospitalized 2.5 days; Case 15: Lidocaine, 10 mg/liter (emergency treatment)

Table 2. Drug Concentrations at Various Sites after Fatalities Attributed to Propoxyphene^a

Case	Specimen	Pro- oxy- phene	Norpro- oxyphene	Cyclic Dinorpro- oxyphene
		mg/liter, or mg/kg wet wt		
1	Blood	4.9	1.4	0.1
	Urine	7.8	7.7	0.2
	Liver	229.4	73.2	3.5
	Brain	14.7	4.0	0.0
2	Blood	4.9	2.3	0.0
	Urine	1.5	1.6	0.0
	Liver	32.7	24.2	0.6
	Brain	25.2	6.3	0.0
	Gastric contents	3348.7	31.8	21.1
3	Blood	4.1	5.9	0.2
	Urine	13.1	25.2	0.0
	Liver	140.9	45.9	0.0
	Brain	13.6	5.5	0.4
	Gastric contents	800.8	19.1	0.0
4	Blood	2.6	2.5	0.2
	Urine	60.2	286.7	2.7
	Liver	132.9	63.1	2.4
5	Blood	1.1	5.1	0.3
	Urine	1.9	19.4	0.4
	Liver	5.7	48.7	10.0
	Brain	2.8	9.1	0.9
	Gastric contents	251.6	73.4	2.2
6	Blood	3.5	4.0	trace
	Liver	59.9	45.7	trace
	Gastric contents	1323.5	19.6	—

^a Specimens analyzed by analysts at Eli Lilly & Co.

sential that no other cause of death be apparent and that the blood contain at least 1 mg of the parent drug, propoxyphene, per liter. The gas-chromatographic method used was essentially that of Nash et al. (8).

Results and Discussion

Initial extraction of the blood at pH 9.8 removes both propoxyphene and norpropoxyphene. If the pH is adjusted to a value exceeding 10 before the final extraction with chloroform, norpropoxyphene is converted into norpropoxyphene amide. Converting norpropoxyphene to norpropoxyphene amide prevents the appearance of extraneous gas-chromatographic responses by norpropoxyphene. Both propoxyphene and norpropoxyphene amide should be detectable in blood if propoxyphene has been ingested; it should not be necessary to form any other derivative for positive identification. Incubating the strongly alkaline solution (7) rather than immediately extracting without incubation (6, 8) made no notable difference in results.

Concentrations of propoxyphene and its metabolites in blood after therapeutic doses. Bioavailability data (1) on various propoxyphene HCl products show that after a 65-mg oral dose the maximum concentration of propoxyphene in blood in 2 h is 0.05 to 0.1 mg/liter, and that this concentration is doubled to about 0.2 mg/liter after the ingestion of 195 mg of the hydrochloride or 300 mg of the napsylate (7). Correspondingly, a concentration of 0.3 mg of norpropoxyphene per liter is produced by the above doses. With its much shorter half-life (12 h), the propoxyphene concentration declines much faster than that of norpropoxyphene, which has a half-life of 36 h. The blood of patients consuming as much as 800 mg of propoxyphene napsylate per day for four days contained, per liter, 0.8–1.2 mg of norpropoxyphene, 0.1–0.2 mg of propoxyphene, and 0.04–0.1 mg of cyclic dinorpropoxyphene on the fourth day (8).

Concentrations in cases of fatal overdose. After reviewing a number of deaths in which propoxyphene appeared to be the cause of death, I consider the minimum fatal concentration of propoxyphene to be about 1 mg/liter of blood, which is about fivefold the high therapeutic concentration (Table 1). The fact that norpropoxyphene may also reach this concentration after large therapeutic doses demonstrates the need to be able to determine it separately. The relative amounts of propoxyphene and norpropoxyphene may aid in determining the time the dose was taken. Care is necessary in drawing such conclusions, because a person who has been taking the drug for some time should have residual norpropoxyphene present in the blood, and this obviously could cause some confusion. The amounts of cyclic dinorpropoxyphene and of dinorpropoxyphene present in blood are too small to be of importance. Table 2 gives data on their concentrations in other specimens, but evidently not much is to be gained from such information. A large amount in the gastric contents indicates massive ingestion. Urine can be rapidly analyzed by the EMIT immunoassay procedure. Propoxyphene was detected in a subject's urine within 3 h and for as long as 10 h after oral ingestion of 200 mg of propoxyphene napsylate. Hepatic tissue may be examined for propoxyphene instead of blood if the blood specimen is needed for some other determination.

Acute salicylism does not appear to have been a serious factor in our cases, which now number over 100. Only case 11 (Table 1) had a rather high concentration

of salicylate in the blood, 280 mg/liter, and there was also a rather high concentration of ethanol, 2.1 g/liter. The blood in case 12 contained 3 g of ethanol per liter. Undoubtedly these other drugs played a role in the deaths, but I doubt that the deaths would have occurred without the propoxyphene.

Deaths attributed to other causes. Propoxyphene was found in the blood in significant concentrations in some instances where death was attributed to other causes, but the concentration of propoxyphene in such cases was usually less than 1 mg/liter of blood.

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