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Quantitation of Propoxyphene and Its Major Metabolites in Heroin Addict Plasma after Large Dose Administration of Propoxyphene Napsylate

J. FRANK NASH ˣ, I. F. BENNETT, R. J. BOPP, M. K. BRUNSON, and H. R. SULLIVAN

Abstract □ A sensitive and specific GLC assay method was developed for the determination of propoxyphene, its major metabolite norpropoxyphene, and lesser known metabolites cyclic dinorpropoxyphene and/or dinorpropoxyphene in plasma of heroin addicts administered up to 800 mg of propoxyphene napsylate. The assay used a mass internal standard of pyrroliphene. The compounds were extracted from pH 9.8 carbonate-buffered plasma with butyl chloride, back-extracted into acidified water which was then washed with hexane, and reextracted with chloroform from the aqueous phase made basic. Quantitation of the drug and its metabolites was accomplished by temperature-programmed GLC. Absolute identification of the compounds chromatographed was completed by GLC–mass spectrometry.

Keyphrases □ Propoxyphene and metabolites—GLC analysis in heroin addict plasma □ Norpropoxyphene and cyclic dinorpropoxyphene—GLC analysis in heroin addict plasma after propoxyphene napsylate administration □ Dinorpropoxyphene (cyclic) and norpropoxyphene—GLC analysis in heroin addict plasma after propoxyphene napsylate administration □ GLC–mass spectrometry—analysis, propoxyphene and metabolites in heroin addict plasma

Propoxyphene hydrochloride[1] has been prescribed widely for the symptomatic relief of mild or moderate pain. Metabolic studies were conducted using radiocarbon-labeled propoxyphene (1) and with deuterium-labeled drug and GLC–mass spectrometry (2).

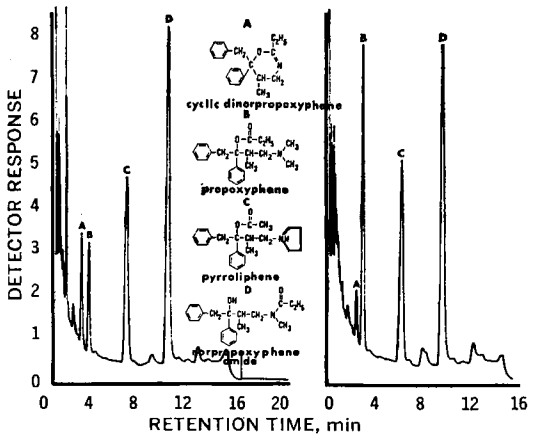


Figure 1—*Gas-liquid chromatogram (flame-ionization detector) of human plasma extracts. Left: blank plasma spiked with: Compound A, 100 ng/ml; Compound B, 100 ng/ml; Compound C, 250 ng/ml; and Compound D, 500 ng/ml. Right: patient's plasma after dose of 200 mg propoxyphene napsylate.*

The 2-naphthalenesulfonate[2], another salt of propoxyphene, has been marketed as a therapeutic agent equally as effective as the hydrochloride (3–6). The use of propoxyphene napsylate in large doses for the treatment of heroin addicts has been reported (7, 8), as has a GLC method for the determination of propoxyphene in plasma (9).

[1] α-*d*-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-propionoxybutane hydrochloride; Darvon, Eli Lilly and Co.

[2] α-*d*-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-propionoxybutane 2-naphthalenesulfonate; Darvon-N, Eli Lilly and Co.

Table I—Precision and Accuracy in Measurement of Cyclic Dinorpropoxyphene, Propoxyphene, and Norpropoxyphene added to Human Plasma

	Cyclic Dinorpropoxyphene		Propoxyphene		Norpropoxyphene	
	25 ng/ml	100 ng/ml	25 ng/ml	100 ng/ml	125 ng/ml	500 ng/ml
Mean[a]	23 (21–25)	101 (87–116)	20 (19–22)	91 (82–97)	118 (104–149)	524 (455–603)
RSD	15.9%	11.5%	6.4%	6.1%	7.7%	10.3%
RE	−8.0%	+1.0%	−20.0%	−9.0%	−6.0%	+5.0%

[a] Mean of five replicate samples (range).

Table II—Plasma Concentrations of Cyclic Dinorpropoxyphene[a], Propoxyphene, and Norpropoxyphene from Patients Administered Large Doses of Propoxyphene Napsylate

Patient	Days	Dose, Tablets of Propoxyphene Napsylate, mg	Day of Plasma Sample	Concentration of Compounds in Plasma, ng/ml		
				Cyclic Dinorpropoxyphene	Propoxyphene	Norpropoxyphene
1	1–4	800	1	0	0	0
	5–8	600	5	49	110	1194
	9–13	400	9	38	80	869
			12	28	61	627
	14–19	200	19	16	10	67
	20–24	0	24	0	11	24
2	1–4	800	1	0	0	0
	5–8	600	5	51	167	770
	9–13	400	9	45	111	503
	14–19	200	17	22	58	162
			19	21	29	96
	20–24	0	24	0	0	0
3	1–4	800	1	0	0	0
	5–8	600	5	55	228	853
	9–13	400	9	49	79	690
			13	27	33	207
	14–19	200	17	16	0	37
	20–24	0	None	—	—	—
4	1–4	800	1	0	0	0
	5–8	600	5	40	197	910
	9–13	400	9	43	161	983
			12	39	64	669
	14–19	200	17	27	12	174
	20–24	0	None	—	—	—
5	1–4	800	1	0	0	0
	5–8	600	5	107	207	1227
	9–13	400	9	61	54	550
			12	34	36	245
	14–19	200	None	—	—	—
	20–24	0	None	—	—	—

[a] The concentrations reported as cyclic dinorpropoxyphene may represent cyclic dinorpropoxyphene and/or dinorpropoxyphene.

This report presents an assay for propoxyphene and its metabolites, norpropoxyphene[3] and cyclic dinorpropoxyphene[4], in plasma from patients and gives the resultant data. With appropriate modifications, this procedure also has been used for the routine assay of propoxyphene and norpropoxyphene in plasma from subjects receiving therapeutic doses of propoxyphene hydrochloride and propoxyphene napsylate.

EXPERIMENTAL

Reagents—*α-dl*-Cyclic dinorpropoxyphene perchlorate, *α-d*-propoxyphene hydrochloride, *α-d*-norpropoxyphene citrate, and *α-d*-pyrroliphene hydrochloride[5] were synthesized[6]. The last compound was used as the mass internal standard for GLC analysis. All solvents used were analytical reagent quality except chloroform and butyl chloride, which were distilled in glass[7]. GLC packing material, 2% OV-7 on Chromosorb W (HP) (80–100 mesh)[8], and the silylating reagent dimethyldichlorosilane[9] were purchased.

Apparatus—A gas–liquid chromatograph[10] equipped with a flame-ionization detector and 1-mv recorder[11] was used. Teflon-lined screw-caps and disposable 15-ml centrifuge tubes[12] were used throughout the extraction procedure. Tapered 15-ml glass centrifuge tubes[13] previously siliconized were used for evaporation[14] of solvent.

Chromatographic Conditions—The recorder was operated at a chart speed of 0.63 cm/min. Helium carrier gas (flow rate of 60 ml/min) was filtered through 1.83-m × 1.27-cm (6-ft × 0.5-in.) copper tubing filled with pellets of molecular sieve 5A. The filter was preconditioned overnight at 200° with dry nitrogen as the conditioning gas. A glass column[8], 0.61 m (2 ft) × 3 mm i.d., was operated isothermally at 185° for 4 min followed by 4°/min programming to 230° during analyses.

[3] *α-d*-1,2-Diphenyl-3-methyl-4-methylamino-2-propionoxybutane.

[4] *α-dl*-6-Benzyl-2-ethyl-5,6-dihydro-5-methyl-6-phenyl-4*H*-1,3-oxazine. Its chemistry will be discussed in a future publication by H. R. Sullivan.

[5] *α-d*-4-Pyrrolidino-1,2-diphenyl-3-methyl-2-acetoxybutane hydrochloride.

[6] At the Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, Ind.

[7] Burdick and Jackson Laboratories, Muskegon, Mich.

[8] Ohio Valley Specialty Chemical, Inc., Marietta, Ohio.

[9] Pierce Chemical Co., Rockford, Ill.

[10] Model 5700A, Hewlett Packard, Avondale, Pa.

[11] Model 7127A, Hewlett Packard, Avondale, Pa.

[12] Corning Glass Co., Corning, N.Y.

[13] Matheson Scientific Co., Chicago, Ill.

[14] Model 106 N-Evap, Organomation Associates, Shrewsbury, Mass.

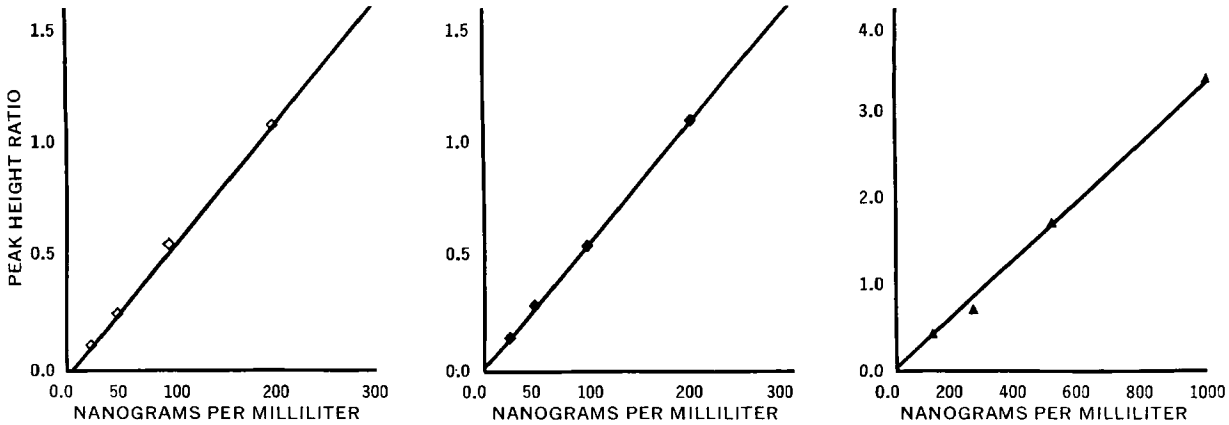


Figure 2—*Calibration curves; relationship between peak height ratio of the compound to the internal standard (pyrroliphene) and the concentration of compound in plasma. Left: cyclic dinorpropoxyphene. Center: propoxyphene. Right: norpropoxyphene.*

Newly packed columns were conditioned by turning the carrier gas on for 2–5 min, heating the column to 300°, and holding without carrier flow for 1 hr. The column was cooled to room temperature, reheated to 250°, and conditioned overnight with carrier gas flowing. The detector temperature was 250°. The oxygen and hydrogen flow rates were 240 and 60 ml/min, respectively.

Under these conditions, the following retention times were observed[15]: cyclic dinorpropoxyphene, 145 sec; propoxyphene, 175 sec; pyrroliphene, 370 sec; and norpropoxyphene amide (rearranged norpropoxyphene formed under basic conditions), 600 sec[16] (Fig. 1). At an electrometer sensitivity of 7.8×10^{-10} A, 1 μg of propoxyphene produced a full-scale deflection.

Procedure—The 15-ml tapered centrifuge tubes were washed with chromic acid cleaning solution, rinsed with water, dried, and siliconized using a 1% solution of dimethyldichlorosilane in toluene[17]. Heparinized blood was centrifuged to separate the plasma[18]. Standard solutions of cyclic dinorpropoxyphene (as the perchlorate), propoxyphene (as the hydrochloride), and norpropoxyphene (as the citrate) were added to 4 ml of blank plasma to give calibration concentrations equivalent to 0, 25, 50, 100, and 125 ng of propoxyphene and cyclic dinorpropoxyphene/ml of plasma and 0, 125, 250, 500, and 1000 ng of norpropoxyphene/ml of plasma.

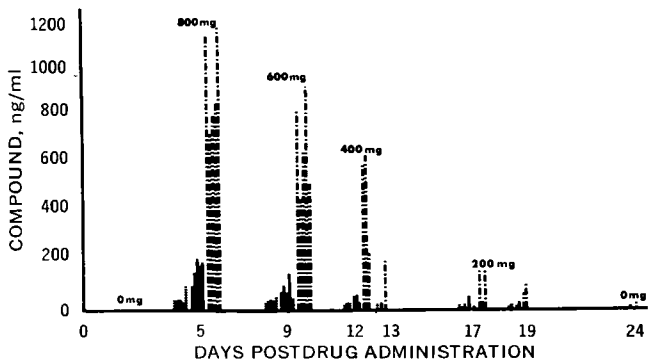


Figure 3—*Plasma concentrations of propoxyphene (—) and metabolites cyclic dinorpropoxyphene (.....) and norpropoxyphene (- - -) after administration of decreasing doses of propoxyphene napsylate to five heroin addicts.*

To each tube were added 0.5 ml of a 2-μg/ml solution of the mass internal standard and 0.5 ml of pH 9.8 carbonate buffer. The mixture was vortexed to ensure uniform distribution of the compounds in the plasma. Using a pipet[19], 10 ml of butyl chloride was added to each tube and the samples were shaken for 2 min and then centrifuged at 2000 rpm for 4 min. The upper organic phase was transferred to a second screw-capped centrifuge tube, and care was taken not to transfer any plasma. Five milliliters of 0.2 *N* hydrochloric acid was added to the samples, which were shaken for 2 min and centrifuged for 4 min. The organic phase was aspirated and discarded. To the aqueous acid was added 5 ml of hexane. The samples were shaken and centrifuged and the hexane was aspirated and discarded. Then 0.6 ml of 2 *N* sodium hydroxide was added with a 1-ml pipet[19] and the samples were vortexed.

After ensuring the pH was 10[20], 10 ml of chloroform was added and the samples were shaken and centrifuged. The upper aqueous phase was aspirated and discarded and the chloroform phase was transferred to a 15-ml siliconized, tapered centrifuge tube. Care was taken not to transfer any of the aqueous phase. The chloroform was evaporated to dryness at 37° under a gentle stream of nitrogen. To the residue was added 20 μl of carbon disulfide–chloroform (1:1) with a 20-μl pipet[21]. The samples were vortexed for 20–30 sec, and 3 μl of each sample solution was injected onto the GLC column.

Plasma from heroin addicts administered propoxyphene napsy-

[15] Methadone chromatographed at 155 sec and could be extracted and quantitated by this procedure.

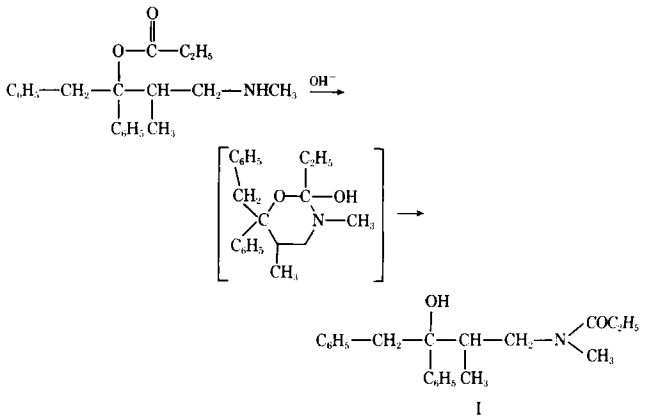
[16] Under the chromatographic conditions described, dinorpropoxyphene amide is not separated from norpropoxyphene amide and any of the former present in the plasma extracts would have been quantitated as norpropoxyphene. If dinorpropoxyphene is present, it will cyclize to an intermediate which dehydrates on column to yield cyclic dinorpropoxyphene. If the extracts are held at pH 12 for 1 hr, the dinorpropoxyphene is essentially all rearranged to dinorpropoxyphene amide. Evidence that cyclic dinorpropoxyphene is a true metabolite of propoxyphene found in plasma is supported by dog data to be presented by Mr. H. R. Sullivan in a forthcoming paper.

[17] This treatment appears to prevent adsorption of the propoxyphene compounds to the glassware.

[18] Fresh plasma or frozen plasma held at −8° for several weeks has been assayed successfully. Alternate freezing and thawing of plasma caused erratic results for propoxyphene and its metabolites.

[19] Repipet, Labindustries, Berkeley, Calif.

[20] Norpropoxyphene, as the secondary amine, could not be quantitated by the GLC procedure. Therefore, it was necessary to treat the samples with strong base, such as an alkali hydroxide, to convert the norpropoxyphene by intramolecular rearrangement through the O to N shift of the propionyl group to the very stable *N*-methyl *N*-propionyl-1,2-diphenyl-3-methyl-2-hydroxy-4-butylamine (I). The amide is readily quantitated by gas chromatography.



I

[21] Precision Pipet, Medical Laboratory Automation, Inc., Mt. Vernon, N.Y.

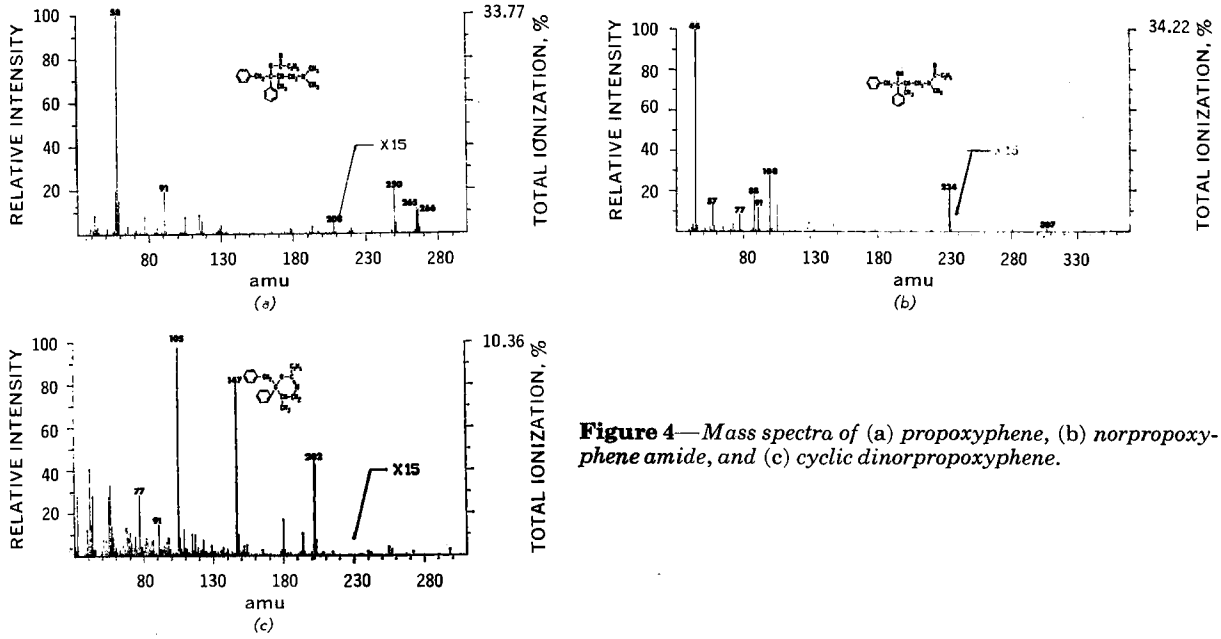


Figure 4—*Mass spectra of* (a) *propoxyphene,* (b) *norpropoxyphene amide, and* (c) *cyclic dinorpropoxyphene.*

late were analyzed similarly after addition of 0.5 ml of the mass internal standard solution.

Following chromatography of the calibration standards, peak height ratios[22] of the propoxyphene compounds to the mass internal standard were calculated. Calibration curves (Fig. 2) were prepared by plotting the peak height ratios *versus* concentrations of drug or metabolites (nanograms per milliliter). Concentrations of cyclic dinorpropoxyphene, propoxyphene, and norpropoxyphene in the sample plasma were calculated from the calibration curves.

Mass spectra of cyclic dinorpropoxyphene, propoxyphene, and norpropoxyphene amide present in the patient's plasma sample extracts were obtained using a gas chromatograph–mass spectrometer[23]. The components present in the extracts were separated using a 1.22-m (4-ft) siliconized glass column of 2.5 mm i.d. packed with 1% W-98 methylvinyl silicone gum rubber[8] on 80–100-mesh Gas Chrom Q, maintained at 160°. The carrier gas, helium, flow was 40 ml/min. The ionizing potential and trap current were 70 ev and 60 μamp, respectively. The temperature of the flash heater was 200°, and the ion source temperature was 290°. Under these conditions, the GLC retention times of cyclic dinorpropoxyphene, propoxyphene, and norpropoxyphene amide were 120, 180, and 780 sec, respectively.

RESULTS AND DISCUSSION

To determine the precision and accuracy of the assay, plasma samples were prepared containing known amounts of cyclic dinorpropoxyphene (as perchlorate), propoxyphene (as hydrochloride), and norpropoxyphene (as citrate) and were assayed by the described procedure (Table I).

Plasma samples were obtained[24] from patients undergoing heroin detoxification with propoxyphene napsylate. Table II reports the plasma concentrations found for propoxyphene and its metabolites. The blood sample was taken before each day's dose.

The histogram in Fig. 3 shows the decrease of propoxyphene and its two major metabolites in patients' plasma as the dose of propoxyphene napsylate is reduced. It is apparent that even when patients are administered large doses of propoxyphene over several weeks, neither the parent compound nor its metabolites accumulate in the blood.

Using the chromatographic conditions previously described for the analysis of plasma samples, methadone was found to elute within 10 sec of cyclic dinorpropoxyphene (see Footnote 15). Positive identification of the cyclic metabolite of propoxyphene in plasma was accomplished by GLC–mass spectrometry. Methadone was identified in a similar manner in plasma samples obtained from patients who were administered methadone. Because of these close retention times, investigators must be careful of false positives for methadone with patients being detoxified with propoxyphene. Separation of the cyclic dinorpropoxyphene and methadone by GLC is accomplished with the 1% W-98 column (120 *versus* 216 sec, respectively).

The mass spectra by which cyclic dinorpropoxyphene, propoxyphene, and norpropoxyphene amide were unambiguously identified are shown in Fig. 4. When the mass spectra of the compounds extracted from patients' plasma were compared with those of the authentic compounds, the fragmentation characteristics were identical.

The mass fragmentation pattern of propoxyphene (Fig. 4*a*) does not show an M^+ at 339 amu[25]. The M − 73 fragment seen at 266 amu represents the loss of the propionyloxy group. The fragment of 265 amu represents the loss of propionic acid (M − 74) from the molecular ion; the additional proton has been shown by deuteration to arise from the benzyl methylene group. The additional fragments observed are the loss of propionic acid plus a methyl group at 250 amu, M − (74 + 15), and the loss of the propionyloxy and dimethylaminomethyl moieties, M − (73 + 58) at 208 amu. The base peak in the spectrum is that of the dimethylaminomethyl ion of 58 amu. The ion at 91 amu represents the benzyl group and is a fragment common to propoxyphene and all of its metabolites.

The mass spectrum obtained from the alkaline rearranged norpropoxyphene (norpropoxyphene amide) is shown in Fig. 4*b*. Again no molecular ion at 325 amu is observed. A small ion at 307 amu is observed and represents the loss of water from the parent ion. The fragment at 234 amu (M − 91) arises by the loss of the benzyl group from the parent ion. The base peak in the spectrum is at 44 amu and represents the methylaminomethyl group. Other fragments observed are those of the propionyl group, 57 amu; the phenyl group, 77 amu; the benzyl group, 91 amu; the *N*-propionylmethylamino group, 100 amu; and the *N*-propionylmethylammonium ion, 88 amu.

Figure 4*c* shows the mass spectrum of cyclic dinorpropoxyphene. Again, no molecular ion is detected. The M − 91 fragment seen at 202 amu results from the loss of the benzyl group from the molecular ion. The major ion at 147 amu reflects the combined loss of the benzyl and the C_2H_5— C^+=N moieties, M − (91 + 55). The most abundant ion is at 105 amu and represents the C_6H_5—C^+=O

[22] Results were virtually unaffected when relative peak areas were used instead of relative peak heights.

[23] Model 9000, LKB-Produkter, Brommo, Sweden.

[24] Dr. F. S. Tennant, Jr.

[25] By use of chemical ionization mass spectrometry, the molecular ion was obtained by Mr. J. L. Occolowitz, The Lilly Research Laboratories.

ion. Ions at 77 and 91 amu represent the phenyl and benzyl groups, respectively.

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Mr. R. N. Booher and Mr. W. W. Turner, Chemical Research, Lilly Laboratories, synthesized the norpropoxyphene citrate and cyclic dinorpropoxyphene perchlorate. Plasma samples for this study were supplied by Dr. Forest S. Tennant, Jr., University of California at Los Angeles. The authors also thank Mr. W. E. Legan for his analysis of the plasma samples.

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Intersubject Variation in Absorption of Digoxin in Normal Volunteers

DAVID H. HUFFMAN [*x], CARL V. MANION [‡§], and DANIEL L. AZARNOFF [‡]

Abstract □ The absorption of oral digoxin preparations was evaluated following single-dose administration of 0.5 mg of digoxin to 16 normal volunteers in a randomized crossover design. Absorption was estimated using the cumulative excretion of digoxin in urine for 7 days and the area under the 24-hr serum digoxin concentration curve (*AUC*). Significant intersubject variability was observed with both parameters, but this variability was greater for the *AUC*. After intravenous administration, the 7-day digoxin excretion was 68% of the dose. The elixir and a rapid dissolution tablet were significantly better absorbed (84.5 and 77.8%, respectively) than was a slow dissolution tablet (66.7%), as reflected by the fraction of the amount excreted in the urine following intravenous administration of the same dose. There was a highly significant correlation between the cumulative digoxin excretion in urine during the first 2 days compared to 7 days ($r = +0.972$, $p < 0.001$). Bioavailability of oral digoxin preparations can be reliably determined by comparison of the cumulative 2-day excretion of digoxin following a single dose.

Keyphrases □ Digoxin oral preparations—bioavailability in humans, intersubject variations □ Bioavailability of digoxin oral preparations—estimated using cumulative excretion in urine and area under serum concentration curve, intersubject variations □ Absorption of digoxin oral preparations—intersubject variations

The bioavailability of oral digoxin preparations has been studied using various protocols. Clinically important differences in bioavailability have been demonstrated among tablet preparations (1–5). Single-dose studies (1, 4–6) and steady-state studies (7) have used the peak serum concentration, the area under the serum concentration *versus* time curve (*AUC*), and the cumulative excretion of digoxin in the urine to estimate the absorption of oral digoxin preparations. Since there has been no complete agreement on the standard method for estimating digoxin bioavailability, and because a larger study was needed to determine the degree of intersubject variability, the bioavailability of digoxin from three oral preparations relative to an equivalent intravenous dose was determined in 16 normal volunteers in a randomized crossover design.

EXPERIMENTAL

Sixteen healthy hospital employees, 10 females and six males (ages 21–33), volunteered for the study. Written consent was obtained after discussing with each subject the inconveniences and hazards reasonably to be expected. All subjects had normal history and physical examinations and no evidence of cardiac, hepatic, renal, or GI disease.

After an overnight fast, 0.5 mg of digoxin was administered to each volunteer on four occasions, each 2 weeks apart. This interval allowed for the essentially complete elimination of digoxin given in the previous study. The following dosage forms were administered to each volunteer in a random sequence:

1. Two 0.25-mg digoxin tablets (I)[1,2]
2. Two 0.25-mg digoxin tablets (II)[3]
3. Ten milliliters (0.05 mg/ml) of a digoxin elixir (III)[4]
4. Two milliliters (0.25 mg/ml) of parenteral digoxin (IV)[5]

The dissolution rates of the tablets were determined by the method described by Lindenbaum *et al.* (8).

The digoxin tablets and elixir were given orally with 200 ml of water. The parenteral solution was administered intravenously over 5 min. Regardless of the route of administration, the subjects

[1] Lanoxin, Lot 474-G, Burroughs Wellcome.

[2] The dissolution of the tablets of the two Lanoxin lots resulted in 85% digoxin dissolved in 1 hr for the 474-G tablet and 65% for the 991-F tablet (R. Cresswell, personal communication). These tablets were taken from regular production runs.

[3] Lanoxin, Lot 991-F, Burroughs Wellcome.

[4] Lanoxin, Lot 816-G, Burroughs Wellcome.

[5] Lanoxin, Lot 062-F, Burroughs Wellcome.