(11) F. Bergman, P. A. Heedman, and W. Vander Linden, *Acta Endocrinol.*, **53**, 256(1966).
(12) R. C. Northcutt, J. N. Stiel, J. W. Hollifield, and E. G. Stant, Jr., *J. Amer. Med. Ass.*, **208**, 1857(1969).
(13) R. Saral and V. L. Spratt, *Arch. Int. Pharmacodyn. Ther.*, **167**, 10(1967).
(14) W. H. Johns and T. R. Bates, *J. Pharm. Sci.*, **61**, 730(1972).
(15) "Difco Manual," 9th ed., Difco Labs., Detroit, Mich., 1953, pp. 203–206.
(16) T. B. Platt and W. E. Brown, E. R. Squibb and Sons, New Brunswick, N. J., personal communication.
(17) "Encyclopedia of Industrial Chemical Analysis," vol. 5, S. Snell and J. Hilton, Eds., Interscience, New York, N. Y., 1967, pp. 513, 514.
(18) G. A. Portman, in "Current Concepts in the Pharmaceutical Sciences: Biopharmaceutics," J. Swarbrick, Ed., Lea & Febiger, Philadelphia, Pa., 1970, p. 18 *ff*.

ACKNOWLEDGMENTS AND ADDRESSES

Received August 11, 1971, from the *Division of Pharmaceutics, School of Pharmacy, University of Connecticut, Storrs, CT 06268*
Accepted for publication January 17, 1972.
Presented in part to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, San Francisco meeting, March 1971.
Supported in part by Grant 076 from the University of Connecticut Research Foundation, Storrs, CT 06268, and by a National Institutes of Health Fellowship (FO1-GM-45,855).
* Present address: Bristol Laboratories, East Syracuse, N. Y.
▲ To whom inquiries should be directed.

Physiological Disposition of Fenoprofen in Man II: Plasma and Urine Pharmacokinetics after Oral and Intravenous Administration

ALAN RUBIN▲, BRUCE E. RODDA, PATRICIA WARRICK, ANTHONY S. RIDOLFO, and CHARLES M. GRUBER, Jr.

Abstract □ Two studies of *dl*-2-(3-phenoxyphenyl)propionic acid or fenoprofen are described. In these studies, the pharmacokinetic parameters of fenoprofen administered orally and intravenously were compared first and then urine and plasma kinetics were compared. The results indicate that: (*a*) fenoprofen is rapidly and efficiently absorbed from the GI tract; (*b*) fenoprofen is extensively metabolized, and it and its metabolites are rapidly eliminated from the body by the kidneys; and (*c*) good agreement exists between plasma and urinary kinetics.

Keyphrases □ Fenoprofen—urinary and plasma kinetics compared after oral and intravenous administration, major urinary metabolites identified, man □ *dl*-2-(3-Phenoxyphenyl)propionic acid—urinary and plasma kinetics compared after oral and intravenous administration, major urinary metabolites identified, man □ Urinary kinetics, fenoprofen—compared to plasma kinetics, major metabolites identified, man □ Fenoprofen glucuronide—major urinary metabolite of fenoprofen, man □ 4′-Hydroxyfenoprofen glucuronide—major urinary metabolite of fenoprofen, man

Results of initial pharmacokinetic studies of *dl*-2-(3-phenoxyphenyl)propionic acid or fenoprofen were reported previously (1). In that study, fenoprofen was administered orally to human subjects as the sodium or calcium salt, and a rapid appearance of fenoprofen in plasma was observed. The plasma disposition curve was compatible with a two-compartment open model. However, a significant peripheral ("tissue") compartment was not detected in that case, and a one-compartment model satisfactorily described the plasma kinetics of orally administered fenoprofen. In preliminary studies wherein sodium fenoprofen was administered intravenously, a two-compartment model seemed more appropriate than a one-compartment model.

This paper reports the results of two studies undertaken to extend the comparison of the pharmacokinetic parameters of fenoprofen administered by both the oral and intravenous routes and to provide kinetic information about the urinary excretion pattern of fenoprofen and its metabolites in man.

EXPERIMENTAL

Subjects—Two study designs were used. For each study, four male subjects[1] were admitted to the clinical research ward and examined as described in an earlier publication (1). The volunteers were between the ages of 22 and 31 years, ranging in weight from 65.8 to 69.0 kg. (145 to 152 lb.) and in height from 170.2 to 185.4 cm. (5 ft. 7 in. to 6 ft. 1 in.). Five subjects were Caucasian, and three (A.C., R.W., and M.B.) were Negro. Informed consent was obtained from each subject before participation in a study.

Study 1: Oral and Intravenous Administration—*Design*—Orally administered doses of 250 mg. fenoprofen[2] were assigned to each of four subjects according to the experimental design used previously (1). One week after the oral crossover was completed, all subjects were given 250 mg. fenoprofen intravenously. All medications were administered at 6:00 a.m. after an overnight fast; food was withheld for an additional 2 hr. After receiving the dose, the men were unrestricted in movement and position. Smoking and water consumption were permitted. The subjects were observed carefully during the tests, and no adverse effects were observed.

Sodium fenoprofen for oral administration was formulated in a single capsule; calcium fenoprofen was formulated in two cap-

[1] From the Indiana Reformatory.
[2] All data are expressed in terms of the free acid (fenoprofen); corrections have been made for molecular weight differences.

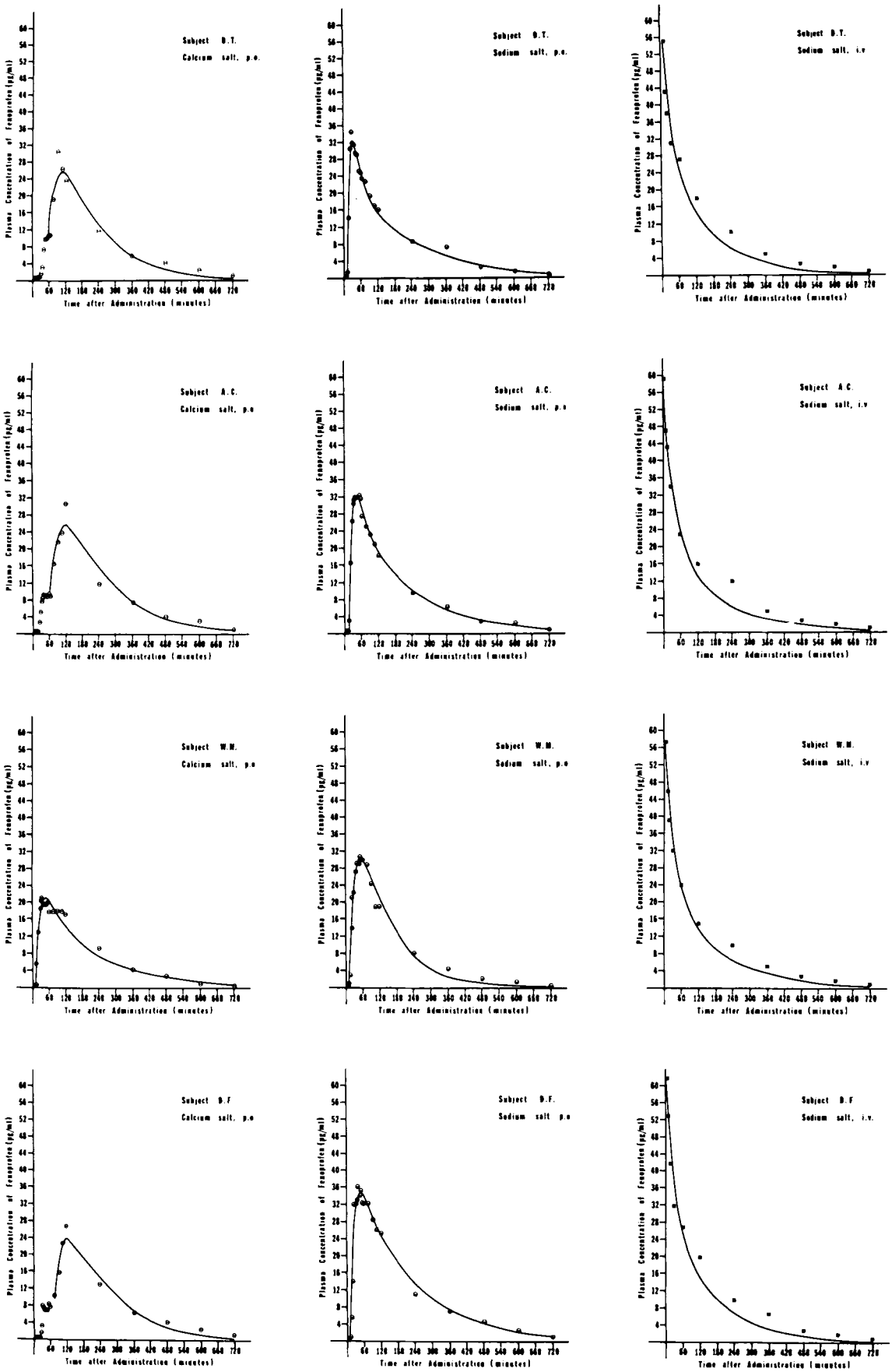


Figure 1—*Predicted and actual plasma concentrations of fenoprofen in four subjects given 250 mg. fenoprofen orally and intravenously. The lines represent concentrations predicted by a two-compartment open model.*

Table I—Pharmacokinetic Parameters for Fenoprofen According to the Two-Compartment Open Model

Salt/Route of Administration	Subject	k_{ab}, min.$^{-1}$	k_{12}, min.$^{-1}$	k_{21}, min.$^{-1}$	k_d, min.$^{-1}$	fD/V_1, mcg./ml.	t_0, min.	V_1, l.	V_2, l.
Sodium/intravenous	A.C.	—	0.014	0.011	0.008	61.0	—	4.1	5.2
	D.F.	—	0.016	0.011	0.008	63.3	—	4.0	5.8
	W.M.	—	0.011	0.010	0.009	58.9	—	4.2	4.7
	D.T.	—	0.018	0.011	0.008	58.3	—	4.3	7.0
Calcium/oral	A.C.	0.021	<0.001	0.002	0.006	45.3	15.0[a]		
	D.F.	0.020	0.002	0.006	0.009	49.6	15.0[a]		
	W.M.	0.039	0.017	0.020	0.009	44.4	10.0		
	D.T.	0.028	<0.001	<0.001	0.007	41.3	10.0[a]		
Sodium/oral	A.C.	0.092	0.007	0.018	0.007	44.7	14.3		
	D.F.	0.048	0.008	0.020	0.007	57.1	10.0		
	W.M.	0.044	0.001	0.001	0.008	46.5	10.0		
	D.T.	0.101	0.014	0.018	0.008	49.0	9.8		

[a] These values are experimentally determined lag times. Precise values could not be estimated in these cases (see text).

sules[3]. Intravenous doses were prepared as sterile solutions of the sodium salt, diluted with 0.9% NaCl to provide a total dose of 10 ml. This solution was injected over a 1-min. interval[4].

Blood and Urine Samples—After medication, blood was collected from each subject and 24-hr. urine samples were collected from two. Blood samples were drawn into heparinized tubes by venipuncture, and the plasma was separated. After oral doses, blood samples were collected at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 75, 90, and 105 min. and at 2, 4, 6, 8, 10, 12, and 14 hr. After intravenous doses, samples were collected at 5, 10, 15, and 30 min. and at 1, 2, 4, 6, 8, 10, 12, and 14 hr. Samples were also collected before medication to serve as blanks and to prepare calibration curves. These curves were prepared with each set of analytical determinations from data in which predetermined amounts of fenoprofen or 4′-hydroxyfenoprofen were added to plasma or urine and subsequently extracted.

1. Fenoprofen in plasma—Fenoprofen content was measured in hexane extracts of 1-ml. aliquots of deproteinized plasma as the trimethylsilyl ester using the GLC method of Nash *et al.* (2).

2. Fenoprofen in urine—Urine was adjusted to pH 4 with hydrochloric acid. Aliquots of 0.25 ml. were pipeted into tubes containing 15 mcg. of internal standard, *dl*-2-(4-phenoxyphenyl)-valeric acid. The samples were extracted and assayed for fenoprofen as already described.

3. Fenoprofen glucuronide in urine[5]—To 0.25 ml. of urine, adjusted to pH 5 with hydrochloric acid, was added 500 units of β-glucuronidase[6] and 0.1 ml. of 0.2 *M* sodium acetate buffer, pH 5. These samples were incubated for 18 hr. at 37° with gentle shaking[7]. After incubation, 15 mcg. of internal standard was added, and the samples were extracted and assayed for fenoprofen content. The amount of fenoprofen excreted as the glucuronide was calculated from the difference between the amounts of fenoprofen present before and after enzymatic hydrolysis.

4. Acid-labile conjugate(s) of fenoprofen in urine—Samples of 0.25 ml. urine were made 6 *N* in sulfuric acid and heated for 30 min. in a boiling water bath. Afterward, 15 mcg. of internal standard was added, and the samples were extracted and assayed for fenoprofen. Levels of urinary acid-labile conjugates of fenoprofen, other than glucuronide conjugates, were then calculated by subtracting the amount of fenoprofen assayed after β-glucuronidase hydrolysis from the amount assayed after acid hydrolysis.

5. 4′-Hydroxyfenoprofen and its conjugates in urine—To 0.25 ml. urine, adjusted to pH 4 with hydrochloric acid, was added 6 mcg. of internal standard. The extraction and assay for 4′-hydroxyfenoprofen are similar to those for fenoprofen, except that methylene chloride is used for the extraction, and the silation procedure for the GLC assay is performed using a 1:10 dilution in carbon disulfide of several silylating agents in a single formulation[8]. The retention times of the trimethylsilyl esters of the internal standard and of 4′-hydroxyfenoprofen were 6 and 12 min., respectively. The chromatographic conditions were identical to those used for the assay of fenoprofen.

Glucuronide conjugates and other acid-labile conjugates of 4′-hydroxyfenoprofen were hydrolyzed and assayed by procedures analogous to those described for fenoprofen conjugates[9]. To analyze for the presence of sulfate conjugates of 4′-hydroxyfenoprofen in urine, samples were incubated with 50 mcg. sulfatase[10] at pH 5 for 18 hr. at 37°. Assays for 4′-hydroxyfenoprofen were conducted using GLC methods before and after enzymatic hydrolysis to quantitate the sulfate conjugate of 4′-hydroxyfenoprofen.

Results—A two-compartment open model was used to describe the fenoprofen kinetics. Initial estimates of the parameters associated with this model were obtained by exponential stripping. Final estimates were computed by nonlinear least-squares estimation techniques. Only one dosage, 250 mg. fenoprofen, was used; however, similar studies in which 40–500 mg. fenoprofen were administered indicated that the kinetics were dose independent within this dosage range.

The actual concentrations of fenoprofen in the plasma of the four subjects and those predicted by the two-compartment open model after oral and intravenous administration of sodium fenoprofen and after oral administration of calcium fenoprofen are displayed graphically in Fig. 1. This figure reflects the good approximation provided by the two-compartment open model to the actual data gathered following administration of the sodium salt either orally or intravenously. The calcium salt, however, did not exhibit equally good agreement with the two-compartment open model. The plasma concentration curves in three of four subjects exhibited preliminary plateaus between 30 and 60 min. after ingestion. In an earlier study, such plateaus could not be observed because concentrations during the 30–60-min. interval were not recorded. The effect of calcium ions on the integrity of mucosal membranes has been a subject of considerable research interest in recent years and poses the possibility that this ion could contribute to the apparent differences in the absorption of fenoprofen administered as calcium salt as compared to sodium salt. In addition, calcium fenoprofen is less water soluble than sodium fenoprofen. Perhaps differences in dissolution contribute to differential amounts of fenoprofen being absorbed from the intestine. What one might be observing in these plateaus, then, is a distinction between the gastric and intestinal phases of absorption. Studies of fenoprofen absorption from the GI tract showed that fenoprofen is absorbed from both the stomach and small intestine. Another factor that could contribute to the

[3] Excipients were starch USP, microcrystalline cellulose, and fumed silicon dioxide.

[4] Calcium fenoprofen was not injected intravenously because of its relatively poor solubility in aqueous solutions.

[5] A manuscript is being prepared describing studies of the metabolism of fenoprefen and confirmation of metabolite structures by IR and NMR analyses. Evidence indicates that the carboxyl group of fenoprofen (and 4′-hydroxyfenoprofen) is esterified to form the corresponding ester glucuronide.

[6] Ketodase (0.1 ml.), Warner-Chilcott Laboratories, Morris Plains, N. J.

[7] Incubating for 48 hr. with twice the specified amount of β-glucuronidase did not result in further hydrolysis of fenoprofen glucuronide to fenoprofen.

[8] Tri-Sil TBT, Pierce Chemical Co., Rockford, Ill.

[9] Occasionally, using acid-hydrolyzed urine extracts, an unidentified compound interfered with the GLC assay for 4′-hydroxyfenoprofen trimethylsilyl ester. This problem was circumvented by lowering the oven temperature from 180 to 170–175°, thus enhancing the resolution of the peak for 4′-hydroxyfenoprofen trimethylsilyl ester.

[10] K & K Laboratories, Inc., Plainview, N. Y.

Table II—Excretion of Fenoprofen and Metabolites in Human Urine

Subject	Salt/Route of Administration	Percent of Recovered Dose Appearing in 24-hr. Urine Collection as: Fenoprofen	4'-Hydroxy-fenoprofen	Fenoprofen Glucuronide	4'-Hydroxy-fenoprofen Glucuronide	Other Acid-Labile Conjugates
W.M.	Calcium/oral	1	3	41	51	5
	Sodium/oral	1	6	34	49	10
	Sodium/intravenous	1	2	38	53	5
D.F.	Calcium/oral	1	2	43	43	12
	Sodium/oral	1	2	36	46	14
	Sodium/intravenous	1	2	35	42	20
Mean		1	3	38	47	11

aforementioned differences in absorption patterns for the two salts is the excipient-to-drug ratio in capsules containing sodium fenoprofen *versus* calcium fenoprofen. However, in other experiments the excipient ratios were unrelated to differences in absorption of fenoprofen.

To estimate certain pharmacokinetic parameters, it was necessary to ignore concentrations preceding the aforementioned plateaus and to use in the estimation only those concentrations that were believed to have occurred after first-order absorption had begun. Evidence from this and the previous study (1) suggests that a lag time of approximately 10–15 min. transpires before the absorption process starts, or at least until the presence of fenoprofen in plasma can be detected by the GLC method (which is sensitive to about 0.2 mcg. fenoprofen/ml. plasma). These parameter estimates are presented in Table I.

Model parameters derived from the intravenous component of the study provided estimates of V_1, the apparent volume of the central compartment. These estimates were generally uniform, being about 4 l. for each subject, which approximates the plasma volume. If it is assumed that this central compartment volume remains constant when fenoprofen is administered orally, an estimate of f, the fraction of the dose, D, appearing in the plasma as fenoprofen after oral administration, can be obtained from the relationship $(fD)/(V_1)$. The estimate of f following oral administration was less than unity, a representative value being 0.8. This fraction was the same for both salts, supporting the contention of the earlier publication (1) that fenoprofen is equally available from either salt.

The value 0.8 could mean simply that 80% of an oral dose of fenoprofen was absorbed from the GI tract. In the oral case, the amount of fenoprofen actually absorbed from the GI tract may not be reflected accurately by plasma concentrations of unchanged fenoprofen. Concentrations of fenoprofen in plasma may be lower than those after intravenous administration, not only because of the contribution of the absorption parameter but also because of possible metabolism of fenoprofen by the liver on its initial pass through the portal circulation. In this connection, fenoprofen was found to be extensively metabolized in man (Table II). Thus, the metabolism of fenoprofen was important in the elimination of the drug from the body; we believe it is reasonable to expect that when fenoprofen is orally administered, measurements of unchanged fenoprofen in plasma may lead to significant underestimation of the fraction absorbed.

Although not evident from cursory examination of the curves

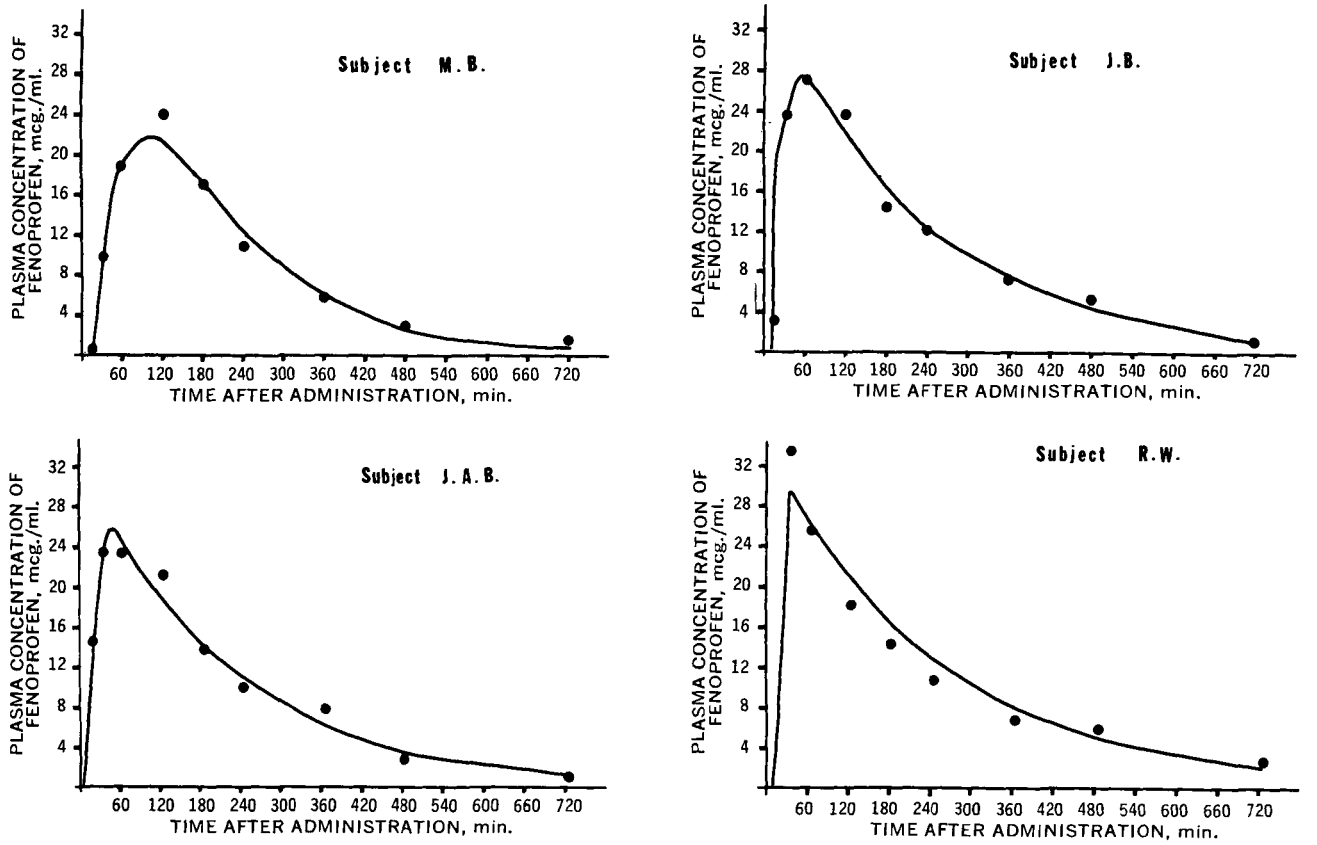


Figure 2—*Predicted and actual plasma concentrations of fenoprofen in four subjects given 250 mg. (50 μc.) fenoprofen-^{14}C orally as the calcium salt. Lines represent concentrations predicted by a one-compartment open model.*

Table III—Parameters of the One-Compartment Open Model for Calcium Fenoprofen

Parameters	Subjects			
	J.B.	R.W.	J.A.B.	M.B.
Fraction absorbed	1.00	0.99	0.85	0.93
Volume of distribution, l.	7.53	7.52	7.11	5.41
Absorption rate constant, min.$^{-1}$	0.08	0.19	0.07	0.02
Elimination rate constant, min.$^{-1}$	0.005	0.004	0.005	0.008
Half-life, min.	139	173	139	87
Lag time, min.	14	0	6	15
Clearance, ml./min.	41	41	48	39
Excretion rate constants × 100, min.$^{-1}$				
Free fenoprofen	0.005	0.004	0.020	0.024
Fenoprofen glucuronide	0.205	0.236	0.135	0.304
Unidentified fenoprofen conjugate	0.030	0.024	0.035	0.144
4′-Hydroxyfenoprofen	0.005	0.004	0.025	0.020
4′-Hydroxyfenoprofen glucuronide	0.200	0.108	0.210	0.136
Unidentified conjugate of 4′-hydroxyfenoprofen	0.075	0.024	0.035	0.104

of Fig. 1, the peaks of the oral sodium salt curves intersect the intravenous curves. This intersection is expected when the two-compartment open model is appropriate and when the kinetics are independent of the route of administration (3, 4). However, in the four subjects given the calcium salt orally, the oral curves reached a peak later than what would be predicted if this relationship (sometimes called the Bateman function) were satisfied. This discrepancy with the calcium salt might have been due to different absorption phenomena, as discussed previously.

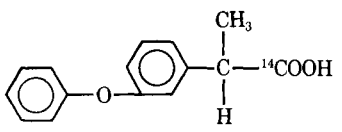
In the earlier study (1), it was not possible to conclude that the two diffusion parameters relating the central and peripheral compartments, *i.e.*, k_{12} and k_{21}, were nontrivial. This could be attributed to inadequate sampling immediately after peak plasma concentrations of fenoprofen had occurred. Since the volume of the peripheral compartment depends on these diffusion rate constants, the volume of the peripheral compartment in that study would not be estimated accurately. In designing the present study, more observations were included in the region of the peak level so that the rate constants and the apparent volume of the peripheral compartment could be estimated more confidently. Estimates of k_{12} and k_{21} in the current study were consistently between 1 and 2%/min., following intravenous administration of sodium fenoprofen. These parameters were more variable following oral administration, again negating confident estimation of V_2 in this case and providing no information to indicate a consistent difference between the two salts with respect to V_2.

The plasma concentrations observed after intravenous sodium fenoprofen indicate the existence of two compartments of nearly equal volumes, although the peripheral compartment was somewhat larger. By assuming f is the same in this study as in the earlier publication (1), the volume of the central compartment is slightly smaller in this study than previously. This was not unexpected because, although a two-compartment open model was used in both studies, the inability to obtain good estimates of k_{12} and k_{21} in the earlier study effectively reduced that model to a single compartment.

The results of this study indicated that:

1. At least 80% of an orally administered 250-mg. dose of fenoprofen was absorbed from the GI tract regardless of the salt form of the drug.

2. A two-compartment open model adequately described the fenoprofen concentrations in plasma; this was true whether fenoprofen was administered intravenously or orally. However, estimates of the volume of the second compartment were quite variable following oral administration, suggesting that a single-compartment open model, in spite of its weaknesses, may be used confidently in the oral case.



I

14C-dl-2-(3-phenoxyphenyl)propionic acid, fenoprofen-14C

3. Fenoprofen is extensively metabolized to fenoprofen glucuronide and 4′-hydroxyfenoprofen glucuronide; small amounts of unchanged fenoprofen, 4′-hydroxyfenoprofen, and unidentified metabolites are excreted.

Study 2: Disposition of Fenoprofen-14C and Its Metabolites—*Design*—Calcium fenoprofen was synthesized with a ^{14}C-label at the carboxyl group (Structure I), a position reported to be metabolically stable in rats (5). The specific activity of this material was 0.25 μc./mg. TLC and GLC of the labeled compound revealed only one major component (>98%).

The dosage forms were capsules containing 200 mg. (50 μc.) calcium fenoprofen-14C, 88 mg. unlabeled calcium fenoprofen (total 250 mg. acid equivalent fenoprofen), and excipients. As before, the capsules were given to the subjects in the fasted state, and food was withheld for an additional 4–6 hr. after dosing.

Blood was drawn at 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 12 hr. after drug administration. Urine samples were collected at 0–2, 2–4, 4–6, 6–8, 8–12, 12–24, and 24–48 hr.[11]. Individual stools for each subject were collected for 72 hr. in unlined paint cans. The samples of plasma and urine were frozen until assayed; feces were refrigerated.

Radiochemical Assays—Samples were analyzed by liquid scintillation techniques using a liquid scintillation spectrometer[12] with external standardization. Samples of plasma, urine, saliva, and washed erythrocytes were counted for 10 min. in 15 ml. of a solution consisting of 0.5% 2,5-diphenyloxazole in 1:1 toluene–2-methoxyethanol[13]. Digestion with Soluene[14] was carried out where necessary. Counting efficiencies exceeded 83%.

Stool specimens were combusted by a modified Schoniger technique (6). After combustion, 10 ml. of 30% ethanolamine in 2-methoxyethanol was added to the sample. After 30 min., 10 ml. of a phosphor solution of 0.5% diphenyloxazole in toluene was added and the samples were counted for 10 min. Counting efficiencies exceeded 75%.

Samples of urine from each collection period were analyzed by GLC and scintillation counting to determine the rate of excretion of fenoprofen and its urinary metabolites.

Pharmacokinetics—In previous studies, it was demonstrated that although a two-compartment model was more realistic from a physiologic standpoint, a single compartment was usually adequate for describing the plasma concentration curve for fenoprofen after oral administration. Also, estimation of the additional parameters of the two-compartment model requires substantially more plasma samples to provide reasonably precise estimates. Therefore, a one-compartment open model with first-order absorption and elimination was considered both appropriate and satisfactory for the purpose of this study.

A fraction, f, of the 250-mg. dose appears in the apparent volume of distribution, V. A lag time, t_0, was included to accommodate

[11] For Subject R.W., urine samples were collected at 0–4, 4–8, 8–12, 12–24, and 24–48 hr.
[12] Beckman model LS-100.
[13] Methyl Cellosolve.
[14] Soluene 100, Packard Instrument Co.

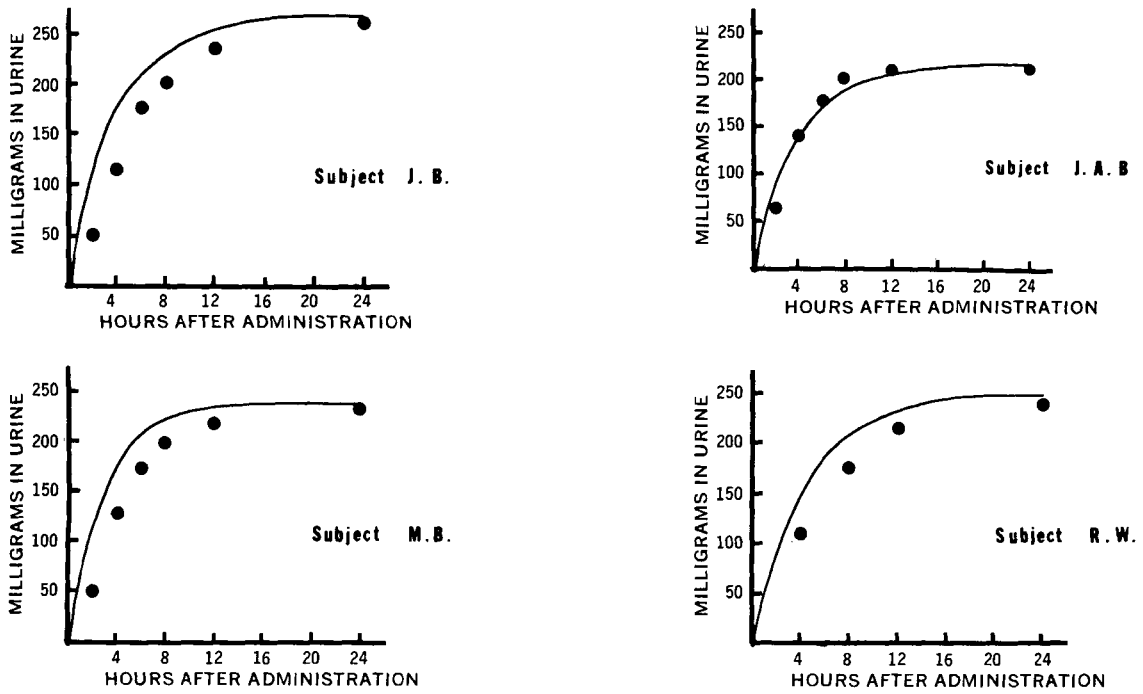


Figure 3—*Relationship between the cumulative amount of fenoprofen plus its metabolites excreted in urine and the time after administration. Lines represent predicted excretion values.*

capsule dissolution and other factors which might delay onset of the absorption process (represented by the first-order rate constant k_{ab}). Six rates of elimination were considered; k_e, k_g, k_c, k_{4f}, k_{4fg}, and k_{4fc} represent the first-order excretion rate constants of fenoprofen, fenoprofen glucuronide, an unidentified fenoprofen conjugate, 4′-hydroxyfenoprofen, 4′-hydroxyfenoprofen glucuronide, and an unidentified 4′-hydroxyfenoprofen conjugate, respectively.

Pharmacokinetic parameters were estimated in two stages. Because detectable levels of metabolites in plasma were not observed, total elimination ($k_e + k_g + k_c + k_{4f} + k_{4fg} + k_{4fc}$) had to be estimated from the observed plasma concentration curve for fenoprofen. Once this and the other parameters of the plasma model (f/V, k_{ab}, and t_0) were estimated, urinary excretion data were used to estimate the six individual excretion rate constants, f, and subsequently V.

Parameters of the plasma model were estimated as in Study 1 and were then used to describe the plasma concentrations of fenoprofen for each of the four subjects (Table III). Figure 2 presents the predicted plasma concentration curves and the observed concentrations. Excellent agreement was obtained between predicted and observed concentrations, the largest deviation being about 3 mcg./ml. This agreement provides a degree of confidence in the derived estimates; further reduction in the sums of squared deviations, which might be achieved by adding a second compartment, would be minimal.

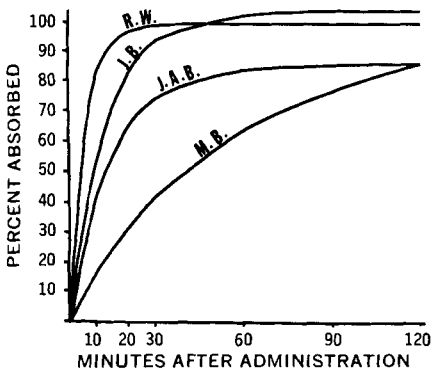


Figure 4—*Percent absorbed–time plot for fenoprofen in four subjects given 250 mg. (50 μc.) fenoprofen-^{14}C orally as the calcium salt.*

Inclusion of sequential urine samples allowed estimation of excretion rate constants and plasma clearance and comparison of parameters common to the plasma and urine. When total urinary excretion (fenoprofen plus metabolites) was predicted from the parameters derived from plasma kinetics, overestimations were consistently observed. However, when one considers that a finite period elapses before excretion begins and then corrects the curve for this, the total urinary excretion pattern is approximated quite well (Fig. 3).

The proportions between each of the six compounds recovered in the urine to the total urinary recovery were multiplied by the elimination rate constant to estimate metabolite excretion rate constants (Table III). If the model for total fenoprofen were satisfactory for the metabolites as well, then the model parameters should provide reasonable approximations of the urinary excretion patterns for individual metabolites. However, in contrast to the total excretion pattern, consistent underestimation was observed in the early phase of the cumulative urinary excretion curves of both fenoprofen glucuronide and 4′-hydroxyfenoprofen glucuronide. This underestimation implies that these metabolites may be formed at a rate greater than that expected from a first-order process. The rate of appearance in urine of the two unidentified acid-labile conjugates was significantly lower than for the glucuronides and was nearly constant over certain intervals for some subjects. Thus, depending upon which metabolites were studied, urinary excretion rates both greater and less than expected from first-order kinetics were observed. When the excretion of total drug is analyzed, these effects probably mask one another so as to present an apparent first-order excretion process overall.

Absorption patterns are presented in Fig. 4, a percent absorbed–time plot. Three of the four subjects absorbed over 80% of the administered dose within 1 hr. after administration. Subject M.B., a relatively slow absorber, took about 2 hr. to accomplish this.

Based upon urinary recovery of fenoprofen and metabolites, at least 85% of the dose was absorbed; two subjects excreted the entire dose. Only small quantities appeared in the feces of two subjects (<2% of the dose over a 48- or 72-hr. collection period); none appeared in the feces of the other two subjects.

Clearance of fenoprofen from plasma was estimated by plotting the urinary excretion rate during each urinary recovery period against the plasma concentration observed at the midpoint of that interval. At equilibrium, this relationship is linear, and the slope of the derived line provides an estimate of plasma clearance. Figure 5 presents these graphs for each of the four subjects. The lines were

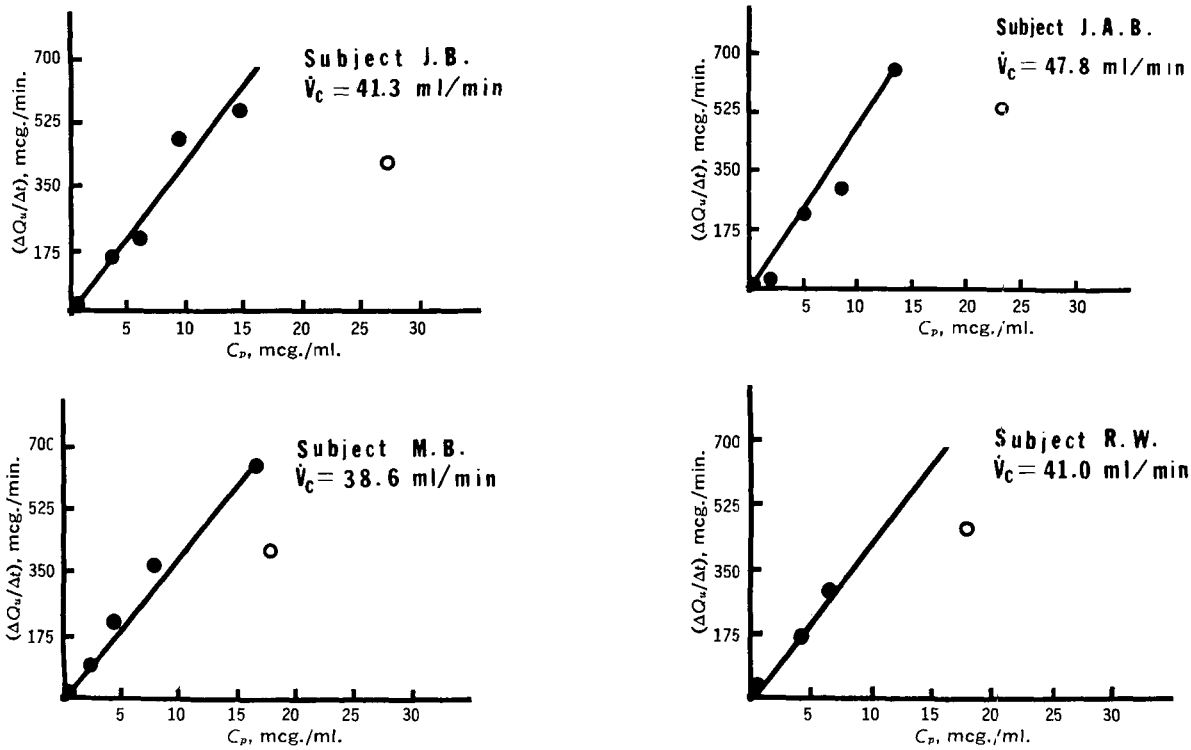


Figure 5—*Relationship between plasma concentration and urinary excretion rates. Each graph contains one outlying point (open circles) which occurred during the absorptive phase; these points were excluded from calculations of clearance.*

constrained to pass through the origin, and slopes were estimated by least squares. Little deviation from linearity was observed, correlation coefficients being greater than 0.95 in all instances. Clearances ranged from 38.6 to 47.8 ml./min., suggesting that fenoprofen undergoes tubular reabsorption. Over 90% of a dose of fenoprofen is metabolized, presumably by the liver, and the plasma is cleared rapidly of metabolites by the kidneys. Because no metabolites of fenoprofen have been observed in plasma, these clearances may be considered estimates of the hepatic clearance rate.

The results of this study indicated that:

1. The overall excretion of fenoprofen is a first-order process, although excretion of individual metabolites may be greater or less than expected from first-order kinetics.
2. Plasma clearance was consistent for the four subjects, being about 39–48 ml./min., suggesting that fenoprofen undergoes tubular reabsorption.
3. Fenoprofen glucuronide and 4′-hydroxyfenoprofen glucuronide are the major urinary metabolites of fenoprofen in man.

REFERENCES

(1) A. Rubin, B. E. Rodda, P. Warrick, A. S. Ridolfo, and C. M. Gruber, Jr., *J. Pharm. Sci.*, **60,** 1797(1971).

(2) J. F. Nash, R. J. Bopp, and A. Rubin, *ibid.*, **60,** 1062(1971).

(3) H. Bateman, *Proc. Cambridge Phil. Soc.*, **15,** 423(1910).

(4) F. H. Dost, "Der Blütspiegel: Kinetic der Konzentrationsaublaufe in der Kreislaufflüsingkeit," Georg Thieme, Leipzig, E. Germany, 1953.

(5) H. W. Culp, *Fed. Proc.*, **30,** 2062(1971).

(6) R. G. Kelly, E. A. Peets, S. Gordon, and D. A. Buyske, *Anal. Biochem.*, **2,** 267(1961).

ACKNOWLEDGMENTS AND ADDRESSES

Received October 26, 1971, from *Eli Lilly and Company, Indianapolis, IN 46202*

Accepted for publication January 19, 1972.

The authors appreciate the assistance of Mrs. Elsie M. Ernst, who prepared the graphs presented in this manuscript. They also acknowledge the advice of Dr. Robert L. Wolen, who helped organize this report. Finally, the cooperation of the nursing staff at the Lilly Laboratory for Clinical Research is gratefully acknowledged.

▲ To whom inquiries should be directed.