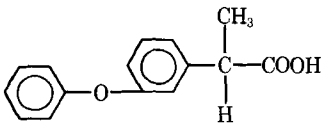
Physiological Disposition of Fenoprofen in Man I: Pharmacokinetic Comparison of Calcium and Sodium Salts Administered Orally

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

Abstract □ Because orally administered *dl*-2-(3-phenoxyphenyl)-propionic acid, fenoprofen, may be useful for maintenance anti-inflammatory/analgesic therapy in man, evaluations were begun of certain pharmacokinetic parameters related to the absorption and disposition of this compound. This study compares these parameters for two salts of fenoprofen. A two-compartment open model was used to analyze plasma concentration data; the model accurately described the plasma levels following oral administration of sodium and calcium fenoprofen. A one-compartment model also provided reasonably accurate descriptions and was used to simulate plasma concentrations in multiple-dose situations from single-dose data. Under the conditions of the study, fenoprofen, administered orally as the sodium or calcium salt, was readily absorbed from the GI tract; however, absorption after the calcium salt was delayed slightly compared to the sodium salt. The bioavailability, distribution, and elimination of fenoprofen appeared to be independent of the salt form of the drug.

Keyphrases □ *dl*-2-(3-Phenoxyphenyl)propionic acid—absorption, distribution, calcium and sodium salts bioavailability, man □ Fenoprofen—absorption, distribution, calcium and sodium salts bioavailability, man □ Absorption kinetics, GI—*dl*-2-(3-phenoxyphenyl)propionic acid (fenoprofen), man □ Bioavailability—calcium and sodium salts of fenoprofen, man □ Plasma levels—fenoprofen, man

Northover (1) showed that some aryl- and alkyl-substituted phenoxyacetic acids exhibited anti-inflammatory properties. One such compound, *dl*-2-(3-phenoxyphenyl)propionic acid, or fenoprofen, exhibited anti-inflammatory and analgesic activities in experimental animals (2) and in man (3–5). The sodium and calcium salts of fenoprofen investigated in the present study are crystalline dihydrates. The chemical structure of fenoprofen is shown here.



fenoprofen

This publication is the first in a series designed to provide basic information about the physiological disposition of fenoprofen in man.

Initially, fenoprofen as the sodium salt was investigated as an anti-inflammatory analgesic. The calcium salt was included later because it was apparently more stable that was the sodium salt, which becomes amorphous and darkened in specific pharmaceutical formulations. Thus, as part of initial studies to describe the pharmacodynamics of fenoprofen in man, it was necessary to compare certain pharmacokinetic parameters of both salts of fenoprofen. This particular study was designed to answer the following questions:

1. What can be learned about the absorption and physiological disposition of fenoprofen in man from the analysis of plasma concentration data after oral administration?
2. How do the sodium and calcium salts of fenoprofen compare pharmacokinetically?

It was anticipated that such information would be useful in developing rational dosage regimens for fenoprofen in man, as well as providing a basic understanding of the physiological disposition of the drug.

The results indicate that fenoprofen, administered as either the sodium or calcium salt, is readily absorbed from the GI tract. The bioavailability, distribution, and elimination of fenoprofen were similar for the two salts, although absorption after the calcium salt was delayed slightly relative to the sodium salt.

EXPERIMENTAL

Subjects—The four subjects[1] were adult males between the ages of 21 and 30 years, ranging in weight from 64.9 to 94.4 kg. (143 to 208 lb.) and in height from 1.72 to 1.91 m. (5 ft. 8 in. to 6 ft. 3 in.). Three subjects were Caucasian; one, J.W., was Negro. Informed consent was obtained from each subject prior to participation in the study. The subjects underwent routine clinical and diagnostic tests with no clinical evidence of illness.

Medication—Each subject ingested a single oral dose of fenoprofen sodium on one occasion and of fenoprofen calcium on another. Two subjects were given the sodium salt initially and the calcium salt 1 week later; the remaining two subjects received the salts in the opposite order. Each dose was equivalent to 250 mg. fenoprofen and was swallowed with at least 180 ml. of water. Fenoprofen sodium was formulated in two capsules, one containing 50 mg. acid equivalent plus 570 mg. cornstarch USP and the other containing 200 mg. acid equivalent plus 382 mg. starch. Fenoprofen calcium was formulated in a single capsule containing 250 mg. acid equivalent plus 222 mg. starch. The medications were administered at 6:00 a.m. after an overnight fast; food was withheld for an additional 6 hr. after administration. No other medication was administered.

After dosing, the men were unrestricted as to movement or position. Smoking and water consumption were permitted. During the tests the subjects were carefully observed. No adverse effects were evident.

Fenoprofen in Plasma—The concentration of fenoprofen in 1-ml. aliquots of plasma was assayed using the GLC method of Nash *et al.* (6). Briefly, this assay involves hexane extraction of fenoprofen from the protein-free supernate of plasma, separation of contaminants by reextraction of fenoprofen into base, acidification, and reextraction of fenoprofen into hexane. After evaporation of the hexane, the fenoprofen content is measured quantitatively as the trimethylsilyl ester. This assay is quite reproducible and is accurate to about 0.4 mcg. fenoprofen/ml. plasma. Blank plasma samples exhibit apparent fenoprofen concentrations of 0.2 mcg./ml. All data are expressed in terms of the free acid.

[1] Four volunteers from the Indiana Reformatory at Pendleton were admitted to the research ward of the Lilly Laboratory for Clinical Research in Indianapolis.

Pharmacokinetics—A preliminary study of fenoprofen, designed to obtain pharmacokinetic information after intravenous administration, indicated that consideration of the body as a single compartment might not adequately describe the plasma kinetics of fenoprofen. Therefore, a two-compartment open model was used to describe the fenoprofen kinetics (7). This model is represented schematically in Scheme I where:

$C_t^{(1)}$ = concentration of fenoprofen in the central (or "plasma") compartment at any time, t
V_1 = apparent volume of central compartment
$C_t^{(2)}$ = concentration of fenoprofen in the peripheral (or "tissue") compartment at any time, t
V_2 = apparent volume of the peripheral compartment
k_{ab} = first-order absorption rate constant
k_{12} = first-order rate constant representing diffusion from the central to the peripheral compartment
k_{21} = first-order rate constant representing diffusion from the peripheral to the central compartment
k_d = first-order rate constant representing disappearance of fenoprofen from the central compartment by metabolism and excretion

This model is based on the following assumptions:

1. A dose (D) of fenoprofen is administered orally, and a fraction (f) of this dose is absorbed at a first-order rate (represented by k_{ab}) following an initial lag time (t_0). The lag time may be a function of dissolution, gastric emptying, *etc.*
2. Once absorbed, free fenoprofen disappears from the central compartment *via* three first-order processes: excretion, metabolism, and diffusion into the peripheral compartment. Because the plasma was analyzed for fenoprofen and not for circulating metabolite, metabolism cannot be distinguished from excretion in the overall disappearance of the drug from plasma. However, studies in progress should allow such distinctions.
3. Diffusion of fenoprofen from the peripheral to the central compartment follows first-order kinetics.

Under the stated assumptions of the two-compartment open model, the following equation describes the concentration of fenoprofen in the central compartment at any time $t > t_0$:

$$C_t^{(1)} = \frac{k_{ab} fD}{V_1}\left[\frac{(k_{21}-\alpha)e^{-\alpha(t-t_0)}}{(k_{ab}-\alpha)(\beta-\alpha)} + \frac{(k_{21}-\beta)e^{-\beta(t-t_0)}}{(k_{ab}-\beta)(\alpha-\beta)} + \frac{(k_{21}-k_{ab})e^{-k_{ab}(t-t_0)}}{(\alpha-k_{ab})(\beta-k_{ab})}\right] \quad \text{(Eq. 1)}$$

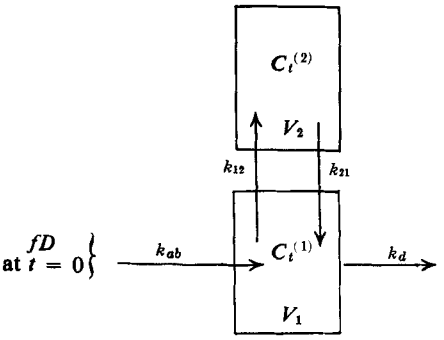
where:

$$\alpha = \tfrac{1}{2}\left[k_{12}+k_{21}+k_d+\sqrt{(k_{12}+k_{21}+k_d)^2-4k_{21}k_d}\right]$$

and:

$$\beta = \tfrac{1}{2}\left[k_{12}+k_{21}+k_d-\sqrt{(k_{12}+k_{21}+k_d)^2-4k_{21}k_d}\right]$$

Initial estimates of parameters in Eq. 1 were derived for each subject–salt pair using an exponential stripping procedure. These approximations were then refined using nonlinear least-squares estimation techniques. Final parameter estimates are presented in Table I.



Scheme I—Two-compartment open model, first-order absorption

RESULTS AND DISCUSSION

Plasma concentrations of fenoprofen were predicted using Eq. 1 and the appropriate experimentally determined constants of Table I. The observed concentrations and those described by the two-compartment model are displayed in Fig. 1. The similarity between actual and predicted concentrations suggests that the parameter estimates are satisfactory under this model. When the sodium salt was given to the four subjects, the characteristic concentration pattern showed a maximum between 0 and 1 hr., as compared with 0.5 and 2 hr. for the calcium salt. At acidic pH, the calcium salt has a slower dissolution rate than the sodium salt; this may explain the delayed appearance of fenoprofen in the plasma following ingestion of the calcium salt.

The observed peak concentration for the sodium salt had a mean of 32 mcg. fenoprofen/ml. plasma (range 18–45); the corresponding value for the calcium salt was 27 (range 23–31) mcg./ml. The actual peak concentrations and the times of their occurrence ($t'_{max.}$) were not observed because of inadequate sampling during this period. However, $t'_{max.}$ values were estimated using the two-compartment model (Table I). Twelve hours after dosage with either salt, the mean concentration had decreased to about 1.5 (range 0.8–2.4) mcg./ml.

The experimental design precluded a precise estimate of the percent of dose absorbed. Although a two-compartment open model was proposed for the kinetic description of fenoprofen, inadequate sampling at certain times effectively reduced the model to a single compartment. Riegelman *et al.* (8) demonstrated that, in such a situation, estimates of V_1 are too large; thus fD/V_1 in this study (35 mg./l.) could be considered a lower bound, and the true value could be much greater. If V_1 were as small as the volume of circulating plasma, about 3.2 l., then the fraction of the dose of fenoprofen appearing unchanged in the plasma following oral administration would be at least 45%. Studies are in progress that include intravenous dosing to allow more confident estimation of this fraction. Among factors affecting the rate and extent of absorption of drugs in solution are their dissociation constants and lipid solubilities of the unionized forms (9–11). In addition, in the case of administration of solid dosage forms, absorption is likely to be dissolution-rate limited.

The absorbed fenoprofen appears to be confined to a single compartment which acts as if it were instantaneously equilibrating with

Table I—Parameter Estimates, Two-Compartment Open Model

Treatment	Subject	Body Weight, kg.	fD/V_1, mg./l.	k_{ab}, min.$^{-1}$	k_{12}, min.$^{-1}$	k_{21}, min.$^{-1}$	k_d, min.$^{-1}$	t_0[a], min.	$t'_{max.}$[b], min.
Fenoprofen calcium	J.H.	95	26.5	0.65	<0.001	<0.001	0.005	27	35
	W.J.	65	36.4	0.03	<0.001	<0.001	0.005	29	101
	R.L.	75	31.0	0.39	<0.001	<0.001	0.006	21	32
	J.W.	65	39.1	0.02	<0.001	<0.001	0.005	15	107
Fenoprofen sodium	J.H.	95	41.3	0.32	<0.001	<0.001	0.011	10	21
	W.J.	65	39.7	0.90	<0.001	<0.001	0.006	10	16
	R.L.	75	20.4	0.06	<0.001	<0.001	0.003	14	67
	J.W.	65	30.5	0.07	<0.001	<0.001	0.004	15	58

[a] t_0 = predicted time lag between drug administration and appearance of measurable amount of fenoprofen in plasma. [b] $t'_{max.}$ = predicted time period to attain peak plasma concentration of fenoprofen.

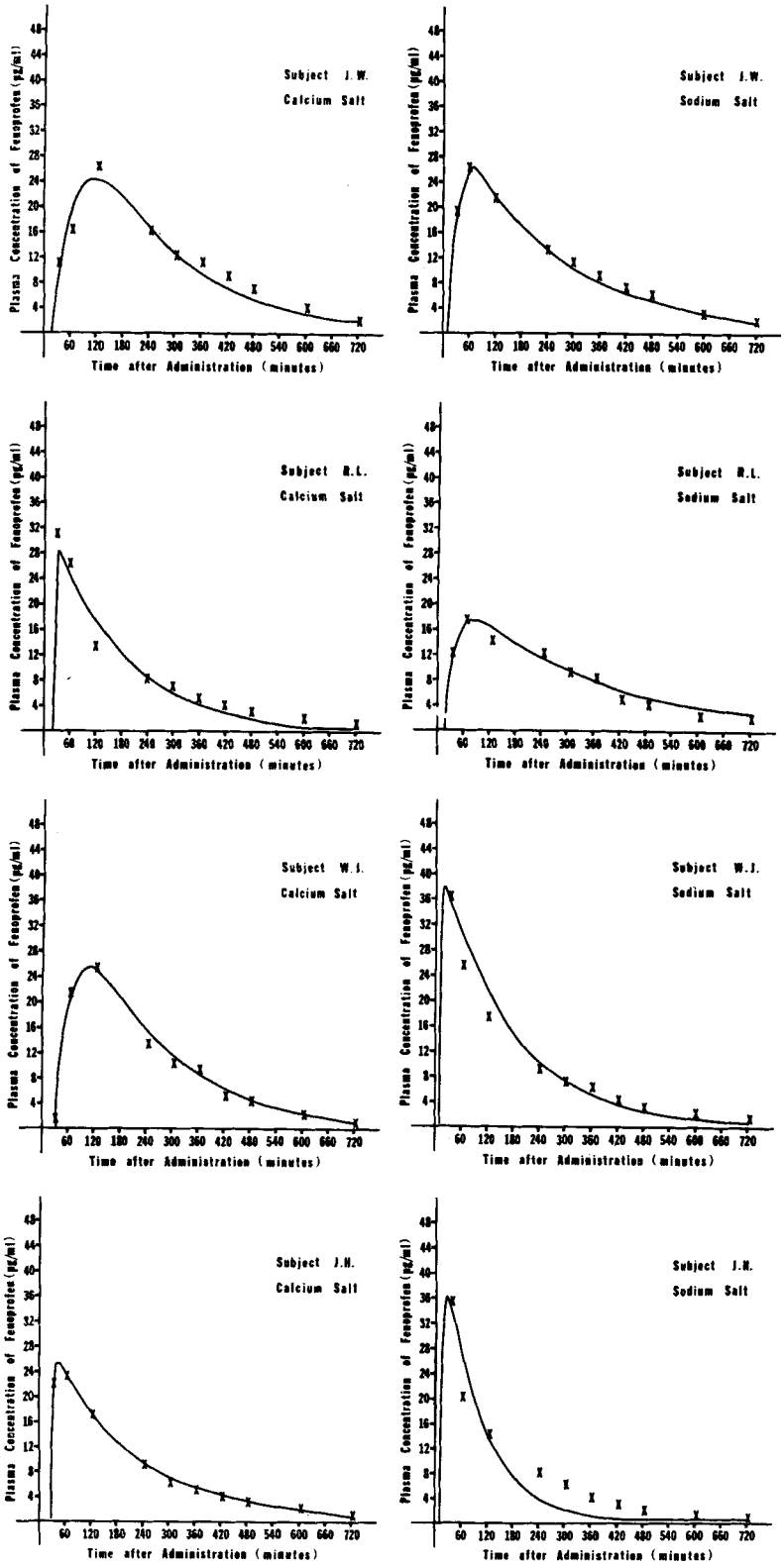


Figure 1—*Fenoprofen was administered orally to four human subjects as the calcium and sodium salts. Each curve describes the concentrations predicted by a two-compartment open-model system; the plotted (×) values represent concentrations determined experimentally.*

the plasma. This could be related to a high degree of binding of fenoprofen to plasma proteins. By using equilibrium dialysis techniques, it was observed that such binding does occur over a wide pH range (5.4–9.4). At concentrations of 40 mcg. fenoprofen/ml. and 4.9 mg. human serum albumin/ml. (*i.e.*, only one-eighth the concentration of albumin present in normal plasma), 99% of fenoprofen was bound to albumin at pH 7.4. Moreover, not only was the binding to protein extensive, but the apparent affinity between the drug and albumin favored the binding process ($K_{assoc.}$ = 30,000).

In other studies, where radioactive plasma samples from subjects who had received ^{14}C-fenoprofen were ultrafiltered, less than 1% of the radioactivity was present in the ultrafiltrate, and over 99% remained in the retentate. Almost all of this radioactivity was accounted for as unchanged fenoprofen.

Distribution of fenoprofen is in accord with a two-compartment model (7, 12), but the distribution into a second compartment appears to be minimal. Table I contains the first-order constants, representing the rates of diffusion of fenoprofen from the central to

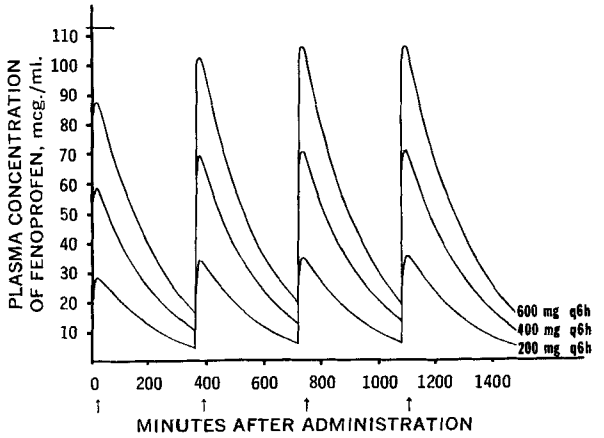


Figure 2—*Hypothetical plasma concentrations of fenoprofen in subjects treated orally with 200, 400, or 600 mg. The dosage is administered every 6 hr., as indicated by the arrows. (See text for assumptions.)*

the peripheral compartment (k_{12}) and the rates from the peripheral to the central compartment (k_{21}). Although these constants are <0.001 (*i.e.*, <0.1%/min.), individual values vary considerably below this limit so that little confidence can be placed in them. Because V_2 (the apparent volume of distribution of the peripheral compartment) depends on the ratio of k_{12} and k_{21}, which are regarded as unreliable, estimates of V_2 would be meaningless. Moreover, if as much as 0.1% of the concentration of fenoprofen in the central compartment were to enter the peripheral compartment per minute, then the effect of this compartment on the system would be minimal. This minimal effect of the peripheral compartment was the same for the two salts[2]. Thus, it appears that the physiological disposition of orally administered fenoprofen could be adequately described by a one-compartment open model in this study.

Figure 1 reflects a general agreement between the experimental and predicted concentrations. In several cases, however, an underestimation of the concentration occurred from 2 to 6 hr. following administration[3]. This underestimation could be explained by an enterohepatic recirculation of fenoprofen, which would be expected to produce a secondary rise in plasma concentration. An enterohepatic recirculation was shown to occur in rats (13), but its occurrence in man is, as yet, unverified.

Fenoprofen concentrations in plasma were predicted for multiple-dose situations. Because the information obtained in this study did not allow adequate description of parameters associated with a peripheral compartment, these predictions were based on a one-compartment open model which assumes that: fenoprofen, upon oral administration, is completely absorbed by a first-order rate process, is distributed uniformly within a single compartment, and is eliminated by a first-order rate process. The parameters of this model were based upon the following representative values: k_{ab} = 0.15 min.$^{-1}$; k_d = 0.005 min.$^{-1}$; f/V = 0.14 l.$^{-1}$; a dosing interval = 6 hr.; and dosages = 200, 400, or 600 mg. of fenoprofen. The kinetic parameters are assumed to be independent of dose in the range under consideration, and single- and multiple-dose plasma levels are considered comparable. Figure 2 depicts the plasma concentrations predicted under these conditions.

Pharmacokinetic calculations (14) indicated that after the second dose, greater than 95% of the equilibrium plasma concentration would be achieved. To reach the equilibrium state at once, a reasonable loading dose would be 1.2 times the maintenance dose (provided, of course, this higher dose was compatible with the pharmacologic effects of the drug).

When a drug is administered repeatedly, $t'_{max.}$ decreases until equilibrium is established. For fenoprofen, however, equilibrium is reached so quickly after the initial dose that clinically this delay is merely a curiosity.

The maximum plasma concentrations to be expected at equilibrium with this regimen at doses of 200, 400, and 600 mg. are 36, 71, and 107 mcg./ml., respectively; corresponding minimum values are 6, 12, and 20 mcg./ml. Thus, the fluctuation ratio ($C_{max.}/C_{min.}$) ranges between 5 and 6. Until sufficient clinical experience is gained with fenoprofen concerning a possible relationship between efficacy and plasma concentrations, the applicability of these predictions to clinical practice must be considered only as theoretical guidelines. However, one additional volunteer (K.H.) was dosed orally every 6 hr. with 500 mg. of fenoprofen as the sodium salt. After 108 doses, the estimated f/V, k_{ab}, and k_d values were virtually identical to the corresponding values obtained after a single dose. Also, the values of the pharmacokinetic parameters agreed quite well with those obtained in this study in which 250 mg. of fenoprofen was used. Thus, in this subject, the kinetics of fenoprofen appeared to be dose independent (in this range), and single-dose data accurately predicted multiple-dose plasma concentrations.

Considerable agreement exists between sodium and calcium fenoprofen with respect to the parameters of the model. Absorption-rate constants, diffusion-rate constants, bioavailabilities, disappearance-rate constants, and half-lives (about 2.5 hr.) were similar for each salt of fenoprofen. Although differentiation between the two salts is uncertain with only four subjects, absorption of fenoprofen administered as the sodium salt began earlier in each subject than absorption following ingestion of the calcium salt. However, there was no consistent indication with respect to k_{ab} values that one salt was absorbed faster than the other. Furthermore, the data are consistent with a conclusion of equivalent availability of fenoprofen from the two salts. By assuming that the apparent volume of the central compartment remains constant for each individual, the parameter fD/V_1 is a measure of the amount of fenoprofen appearing in the central compartment (availability). Subjects J.H. and W.J. exhibited greater availability of fenoprofen from the sodium salt, whereas the reverse was true for Subjects R.L. and J.W. These results would be expected if the two salts were identical; therefore, no additional statistical tests were appropriate.

One subject (W.J.), who had received the sodium salt, exhibited peak concentrations of fenoprofen immediately after a lag time of 10 min. This nearly instantaneous peak negated the estimation of a meaningful value for his absorption parameter, k_{ab}. However, because this value was needed to predict the plasma concentration curve and to provide reasonable estimates of other pharmacokinetic parameters, a k_{ab} value of 0.90 min.$^{-1}$ was selected arbitrarily. Thus, it was assumed that 90% of the available dose was absorbed per minute.

These results indicate that fenoprofen administered as either the calcium or sodium salt is readily absorbed from the GI tract. Absorption of fenoprofen after administration of the calcium salt was delayed slightly relative to the sodium salt. Bioavailability, distribution, and elimination were similar for the two salts.

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[2] Intravenous and oral data from studies in progress, designed to describe more precisely the fenoprofen kinetics, indicate the existence of a nontrivial peripheral compartment.

[3] This underestimation may not appear noteworthy from observation of Fig. 1. However, the "raw" data do indicate a frequent underestimation between 2 and 6 hr. (which is lost in the photographic reduction of individual graphs for reproduction).

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ACKNOWLEDGMENTS AND ADDRESSES

Received April 5, 1971, from *Eli Lilly and Co., Lilly Laboratory for Clinical Research, Indianapolis, IN 46202*

Accepted for publication August 9, 1971.

The authors are indebted to Mr. Larry L. Simms of Eli Lilly and Co. for modifying certain computer programs necessary for collation and analysis of the data. They also thank the ward personnel of the Lilly Laboratory for Clinical Research, Marion County General Hospital, Indianapolis, Ind., for their assistance in this study.

Prediction of Stability in Pharmaceutical Preparations XVI: Kinetics of Hydrolysis of Canrenone and Lactonization of Canrenoic Acid

EDWARD R. GARRETT and CHONG MIN WON

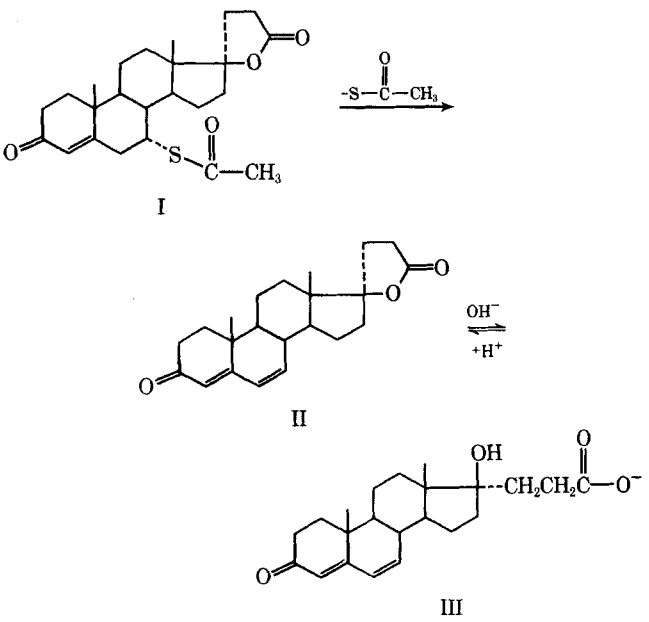
Abstract □ The kinetics of the hydrolysis of the lactone canrenone, 3-(3-oxo-17β-hydroxy-4,6-androstadien-17α-yl)propionic acid γ-lactone, and the lactonization of its corresponding canrenoic acid salt, potassium 3-(3-oxo-17β-hydroxy-4,6-androstadien-17α-yl)propionate, were studied by spectrophotometrically analyzing the chloroform-extracted lactone from canrenoic acid solution. The log *k*–pH profiles in the pH range of 1–12 in various buffer solutions at 25.0, 37.5, 45.0, 60.0, 70.0, and 79.9° show that the kinetics of lactonization include hydrogen-ion attack on the undissociated canrenoic acid molecule and a pH-independent closure of the canrenoate anion. In addition to the hydroxide-ion-catalyzed hydrolysis of the lactone, general base-catalyzed hydrolysis in carbonate buffer solution was observed and attributed to carbonate-dianion attack. The rate constants, equilibrium constants, pKa′ values, solubilities, and Arrhenius' parameters were obtained. Maximum concentrations of canrenoic acid salt to maintain elegant pharmaceutical preparations are given as a function of pH.

Keyphrases □ Canrenone, canrenoic acid—hydrolysis–lactonization kinetics, pH effect, appropriate pharmaceutical preparations □ Pharmacokinetics—canrenone hydrolysis, canrenoic acid lactonization, pH effect □ Hydrolysis—canrenone □ Lactonization—canrenoic acid □ UV spectrophotometry—analysis, canrenone and canrenoic acid

Spironolactone (I), 3-(3-oxo-7α-acetylthio-17β-hydroxy-4-androsten-17α-yl)propionic acid γ-lactone, has been widely used in the treatment of edema that has not responded properly to treatment with conventional diuretics (1). Spironolactone exhibits a specific antagonism to the tendency of the adrenal steroid aldosterone to increase the reabsorption of sodium by reversibly competing with aldosterone at the receptor sites and thus modifying the sodium-retaining electrolyte excretion pattern, which is said to be the mechanism responsible for the production and maintenance of edema (2–4).

Canrenone (II), aldadiene [3-(3-oxo-17β-hydroxy-4,6-androstadien-17α-yl)propionic acid γ-lactone], may be the conjugated diene steroid found in the plasma after the oral administration of spironolactone (5). It may be formed by the elimination of the thioacetate group of spironolactone and may possess similar biological properties as an aldosterone antagonist (Scheme I). As is common with γ-lactones, canrenone (II) is stable in acid and hydrolyzes in alkali to the corresponding canrenoic acid salt (III), potassium 3-(3-oxo-17β-hydroxy-4,6-androstadien-17α-yl)propionate. This study was undertaken to determine the quantitative transformations of canrenone in aqueous solution as a function of pH to supply the basic information necessary for preparing stable aqueous pharmaceutical preparations of canrenone and canrenoic acid.

In addition, it is important to know the ease of the acid–lactone transformation to anticipate the species that may appear in the body under GI and other physiological conditions. As yet, it has not been clarified whether the lactone or the acid, or a metabolite derived from one or the other, is the pharmacologically active compound. The two species also might show different tendencies for protein binding and, hence, influence the distribution pattern of the drug in the



Scheme I