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Pharmacokinetics of Piroxicam, a New Nonsteroidal Anti-inflammatory Agent, Under Fasting and Postprandial States in Man

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The kinetic disposition of piroxicam, under evaluation in man as a new anti-inflammatory drug, was studied in human volunteers given a single oral dose after both overnight fasting and food. Total absorption was uninfluenced by food intake, although the data indicate that food causes some delay in attainment of peak serum levels. The half-life of drug in plasma in the fasting subjects (37.5 ± 2.4 hr) was similar in both the fasting state and after food, suggesting that once-daily dosing may be appropriate for maintaining therapeutic plasma levels. Mean pharmacokinetic parameters for both studies in the fasting state and after meals are volume of distribution divided by availability, 0.140 or 0.136 liter/kg; total plasma clearance divided by availability, 2.68 or 3.12 ml/hr/kg. Approximately 10% of a single dose of piroxicam was eliminated in the urine within 8 days after oral drug administration. Renal clearance of the drug (0.28 ± 0.10 ml/hr/kg) was 10.4% or less of plasma clearance, suggesting that piroxicam is extensively metabolized. In this study one subject showed a reduction in white blood count on the sixteenth day after a 60-mg dose; however, hematology values evaluated in both intra- and intersubject comparisons did not show any other differences in the present study.

KEY WORDS: piroxicam; nonsteroidal anti-inflammatory agent; disposition kinetics; oral administration; absorption; food intake.

INTRODUCTION

Piroxicam, 4-hydroxy-2-methyl-*N*-2-pyridyl-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide, is a new nonsteroidal anti-inflammatory agent structurally unrelated to currently marketed medications for rheumatoid

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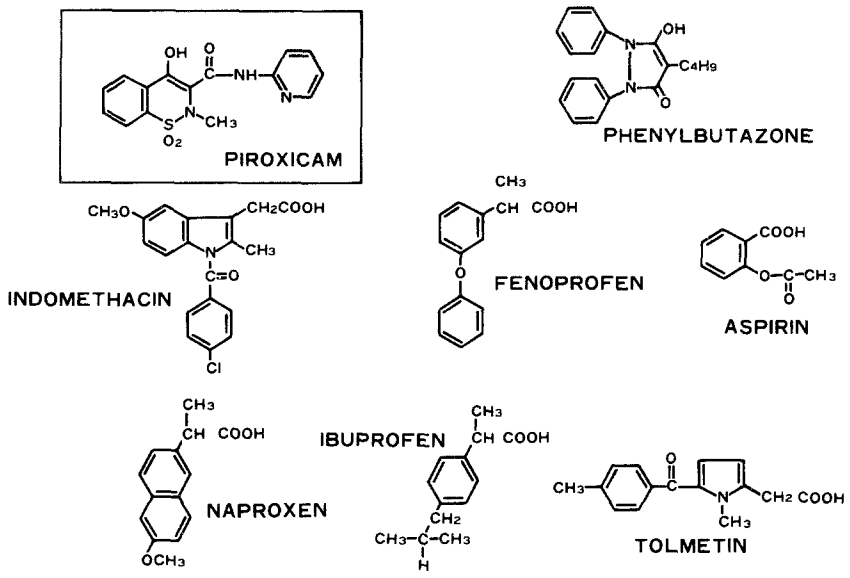

Fig. 1. Chemical structures of piroxicam and other nonsteroidal anti-inflammatory agents.

arthritis (Fig. 1). The pharmacological activity of this drug has been well documented (1). A recent double-blind study (2) has clearly shown that piroxicam given orally in a once-daily dose of 20 or 30 mg was an effective anti-inflammatory drug in patients with active rheumatoid arthritis. Some preliminary disposition studies in animals (3) and in normal man (3,4) have suggested that the pharmacokinetic profiles of piroxicam may be different from those of other nonsteroidal anti-inflammatory drugs recently available (5), and its half-life appears to be much longer.

The development of an assay method for this drug (D. Hobbs, personal communication, Pfizer Central Research, United States) has permitted studies on the kinetic disposition of piroxicam in man. The utility of pharmacokinetics for quantification of drug absorption and excretion is well documented (6,7). The approach permits a prediction regarding drug dosage adjustment in the relation to plasma level and, in addition, allows comparison of the effects of dosage variables on bioavailability and consequently has therapeutic implications (8,9).

The purpose of this report is to describe the pharmacokinetics of piroxicam following oral administration to healthy volunteers. The drug was given both in the fasting and nonfasting states.

METHODS

Subject Selection, Drug Administration, and Specimen Collection

Twenty-two normal healthy volunteers, all male university students, 18–24 years of age and with body weights between 45.0 and 71.0 kg, were selected for the study after informed consent had been obtained. All subjects were considered normal after a physical examination and laboratory studies, including a complete hemogram, urinalysis, fasting blood sugar, serum electrolytes, blood urea nitrogen, serum creatinine, transaminases, alkaline phosphatase, and electrocardiogram.

Seven subjects (group I) were fasted overnight and food was withheld for 4 hr after ingestion of the dose. One of these subjects received two dose levels on two separate occasions 4 weeks apart. All subjects in group I were studied in the metabolic research ward of the National Medical Center Hospital, Tokyo. Venous blood samples were collected at 0 (predose), 0.5, 1, 2, 4, 6, 8, 12, 24 hr, 2, 3, 4, 5, 6, and 7 days after dosing. Urine was collected during the period 0–2, 2–8, 8–24 hr, and daily thereafter up to the seventh day after drug administration. The plasma was separated immediately, and urine volume was recorded. Aliquots were transferred to separate test tubes and frozen at −20°C until analysis.

Fifteen subjects took a standard breakfast (sandwiches, eggs, vegetables, and milk, which contained approximately 20% protein, 40% fat, and 40% carbohydrate) 1 hr before ingestion of an oral dose of either 30 or 60 mg piroxicam (group II). Four of 15 subjects received two dose levels at least 2 weeks apart. Thus in both groups I and II a total of 27 observations were carried out. In group II three or four samples were usually taken in the first 8 hr and on days 1, 2, 4, and 6 after dosing. This sampling schedule was chosen after the long half-life ($t_{1/2}$) was found in the group I study. It was felt that these sampling times would be adequate for the pharmacokinetic analysis.

Piroxicam was given as a capsule containing either 10 or 20 mg of the anhydrous drug. Thirteen subjects received an oral dose of 30 mg of piroxicam (three capsules containing 10 mg), while 14 subjects received 60 mg of piroxicam (three capsules containing 20 mg) with 100 ml water. All subjects in both groups were allowed unrestricted movement and fluid intake except the postprandial condition in group II. Ages (21.3 ± 0.5 and 20.2 ± 0.4 years old) and body weights (61.4 ± 2.0 and 59.0 ± 1.5 kg) were comparable in the two groups.

Drug Assay

The method for the extraction and quantitation of piroxicam (Hobbs, personal communication) was used for drug assay with a minor modification.

Plasma or urine 0.10 ml and 0.5 ml glacial acetic acid were mixed in a 15-ml centrifuge tube, stoppered and incubated for 20 hr at 108°C. After cooling to room temperature, 2 ml of 20% NaOH and 5 ml ethyl acetate were added and the mixture was agitated on a vortex mixer for 20 sec. Following centrifugation, 4 ml of the solvent layer was transferred to a 16- by 100-mm culture tube, and 3 ml 0.1 N H_2SO_4 was added and mixed for 10 sec on a vortex mixer. The solvent layer was aspirated after centrifugation and discarded, and the acidic aqueous layer was subjected to fluorescent measurement. Measurements were made on a Hitachi fluorescence spectrophotometer (MPF-2A) using an excitation wavelength of 310 nm and an emission wavelength of 370 nm. The fluorometric response for calibration was obtained by determining standards at concentrations 0.5, 1.0, 5.0, and 10 μg piroxicam/ml of plasma or 1, 3, 5, and 10 μg piroxicam/ml of urine. Sensitivities were estimated as 0.2 μg/ml for plasma and 0.5 μg/ml for urine samples. When piroxicam was added to plasma or urine at a concentration of 2 μg/ml, the recovery of piroxicam from plasma or urine was $97.1 \pm 2.2\%$ (SD) ($n = 6$) or $74.7 \pm 1.2\%$ (SD) ($n = 6$), respectively.

Pharmacokinetic Analysis

Unweighted piroxicam plasma concentration data (C_t) after single doses of piroxicam were fitted to a one-compartment open model (10) using equation 1:

$$C_t = (FD_0k_a)/V_d(k_a - k_{el}) \times (e^{-k_{el}t} - e^{-k_at}) \quad (1)$$

Three constants can be determined in this equation: k_a, the apparent first-order absorption rate constant (hr^{-1}); k_{el}, the apparent first-order elimination rate constant (hr^{-1}); and V_d/F, the ratio of apparent volume of distribution (liters) to the extent of availability. The other factors in the equation are plasma drug concentration in μg/ml (C), dose in mg (D_0), and time (t) in hr. The BMDR 3R nonlinear regression program of Dixon (11) in conjunction with an IBM 370 model 125 computer was used to calculate the best values of k_a, k_{el}, and V_d/F. The value of F cannot be separated from V_d since an i.v. dose was not available at the outset of the present study. The area under the curve against time (AUC) for each subject after each oral dose was calculated according to

$$[\text{AUC}]_0^\infty = [\text{AUC}]_0^T + C_p^T/k_{el} \quad (2)$$

The $[\text{AUC}]_0^T$ was calculated using the trapezoidal rule where T is the time of the last recorded plasma concentration (C_p). Renal clearance of the drug was calculated by dividing total urinary amount of drug ($[X_u]_0^T$) by $[\text{AUC}]_0^T$. The ratio of total plasma clearance to F was calculated as $(V_d/F) \times k_{el}$. The

predicted time of the peak plasma level after oral administration of piroxicam (t_{max}) was calculated by using equation 3 (12):

$$t_{max} = 1/(k_a - k_{el}) \times \ln (k_a/k_{el}) \quad (3)$$

Hematology Study

Since one subject in group I after the 60-mg dose exhibited a decrease in his white blood cell count (WBC) below the normal range (4000–8000/mm^3), we studied this aspect further. This subject's control WBC was 5000/mm^3. Values were 3800 and 2900/mm^3 at 8 and 16 days after drug administration, respectively, and rose to 4500/mm^3 at 30 days after administration. All subjects in group II and ten normal, age-matched individuals given placebo serving as controls received a complete hematological evaluation before and 1–11 days after drug administration. This included RBC, hemoglobin (Hb), hematocrit (Hct), reticulocyte count, serum haptoglobin, WBC with differentials, and platelet count. Intra- and intersubject comparisons were undertaken to evaluate the data.

Statistical Calculations

All average data are given as the mean ± standard error of mean (SEM). Statistical comparison of mean values was made using Student's t test.

RESULTS

Plasma Level Profiles and Pharmacokinetic Data

Plots of plasma concentrations of piroxicam with time were adequately described by the one-compartment open model in all subjects. Individual and averaged plasma concentration–time curves obtained in group I subjects are shown in Figs. 2 and 3 (left), respectively. The plasma levels of piroxicam on the sixth day after an oral dose of 30 mg were undetectable in one subject in group I.

The overall elimination half-life was 37.5 ± 2.4 hr, and this value was independent of dose. Pharmacokinetic parameters calculated by using equation 1 in group I are given in Table I. The overall values of mean ± SEM are given where considered appropriate. The observed peak levels (C_{max}) and bioavailability indicated by $[AUC]_0^\infty$ were dose dependent. The apparent volume of distribution divided by F for piroxicam was 0.140 ± 0.012 liter/kg.

The cumulative amount of piroxicam excreted unchanged in urine as percent of dose is shown in Fig. 4. Approximately 10% of the total dose was excreted up to 168 hr after drug ingestion. The renal contribution to the

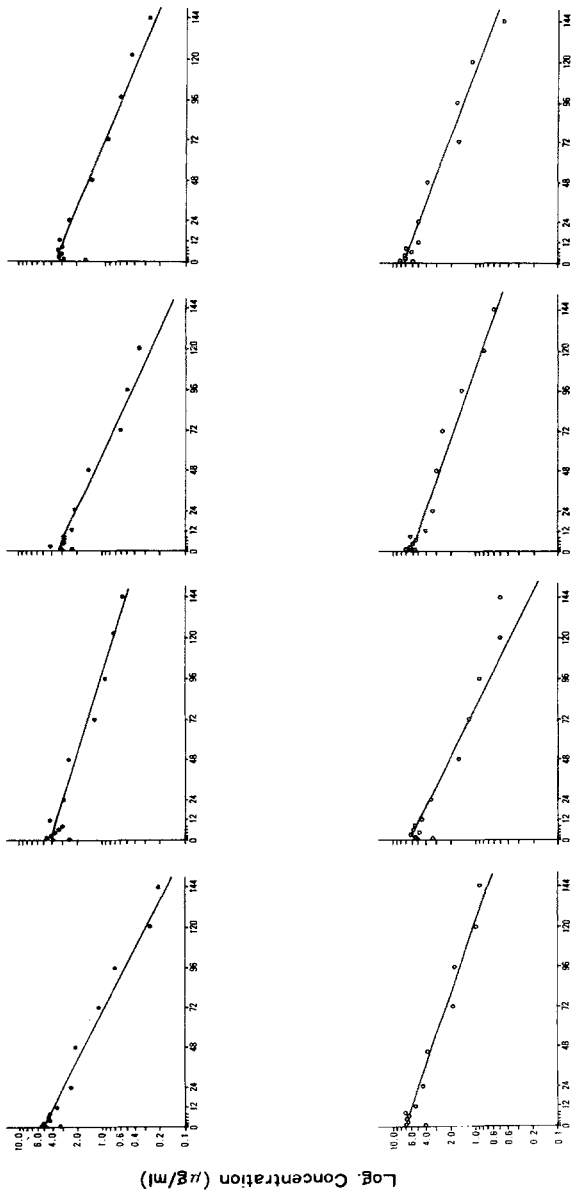

Fig. 2. Individual plots of plasma concentration–time curves after single oral administration of piroxicam either 30 mg (●) or 60 mg (○) in the fasting state (group I).

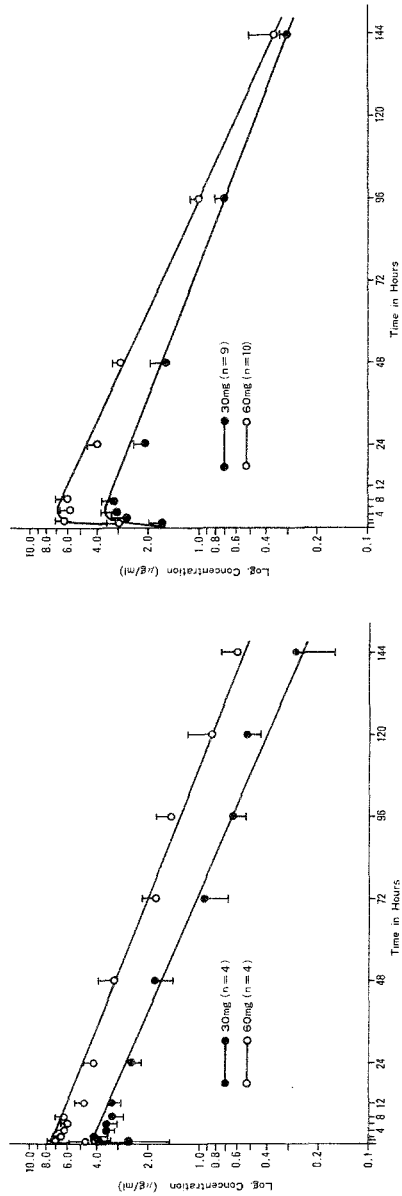

Fig. 3. Averaged plasma concentration–time curves after single oral administration of piroxicam given in the fasting state (left) and after food (right). Data are plotted as mean ±SEM.

Table I. Average Piroxicam Pharmacokinetic Parameters Obtained in Healthy Volunteers in the Fasting State (Group I)[a]

Parameters	Unit	Dose		
		30 mg ($n=4$)	60 mg ($n=4$)	Overall ($n=8$)
$t_{1/2}$	hr	36.5 ± 4.1	38.5 ± 3.0	37.5 ± 2.4
k_{el}	day^{-1}	0.48 ± 0.05	0.44 ± 0.04	0.46 ± 0.03
V_d/F	liters	8.51 ± 0.68	8.45 ± 0.61	8.48 ± 0.56
	liter/kg	0.144 ± 0.012	0.139 ± 0.010	0.140 ± 0.009
Total plasma clearance/F	ml/hr/kg	2.42 ± 0.30	2.85 ± 0.33	2.68 ± 0.23
Renal clearance	ml/hr/kg	0.29 ± 0.12	0.26 ± 0.13	0.28 ± 0.10
f_u	%	12.0 ± 5.9	8.6 ± 3.8	10.3 ± 3.3
$[AUC]_0^\infty$	(μg/ml) × hr	214.8 ± 24.9	388.4 ± 41.4[b]	—
C_{max}	μg/ml	4.43 ± 0.42	7.23 ± 0.51[c]	—
t_{max} observed	hr	2.5 ± 1.2	3.0 ± 1.7	2.8 ± 0.9
predicted[d]	hr	1.2 ± 0.6	0.9 ± 0.4	1.0 ± 0.6
k_a	hr^{-1}	7.86 ± 6.03	7.34 ± 4.67	7.60 ± 1.88

[a] All data are expressed as mean ± SEM. *fu*, Fraction of unchanged drug in the urine after oral dose administered.
[b] $p < 0.05$ from 30-mg dose.
[c] $p < 0.005$, same as above.
[d] Calculated by equation 3.

total plasma clearance from the body was at most 10.4% (i.e., the maximum fraction of total plasma clearance when $F = 1$).

The averaged plasma level profiles of group II subjects are illustrated in the right-hand side of Fig. 3. The pharmacokinetic parameters obtained in group II are seen in Table II. Since no significant pharmacokinetic differences were found, except for $[AUC]_0^\infty$ and C_{max}, between the two dose levels administered, the means ± SEM obtained for 19 observations are shown and compared with those in group I. The $t_{1/2}$ or k_{el}, V_d/F, and total plasma clearance/F calculated as $V_d/F \times k_{el}$ were essentially similar.

Influence of Food on Piroxicam Bioavailability and Absorption

The corresponding peak levels (μg/ml) observed were 4.43 ± 0.42 and 2.98 ± 0.23 ($p < 0.01$) after a 30-mg dose and 7.23 ± 0.51 and 6.39 ± 0.49 ($p < 0.25$) after a 60-mg dose in groups I and II, respectively. Although an effect of food intake on bioavailability indicated by $[AUC]_0^\infty$ appears to be present (Tables I and II), the difference between the two groups did not reach statistical significance ($p < 0.5$). The mean observed peak times were 2.8 and 4.3 hr ($p < 0.05$) in groups I and II, respectively. The time to reach peak concentration calculated using equation 3 was significantly different between fasting and nonfasting subjects ($p < 0.001$). Although individual

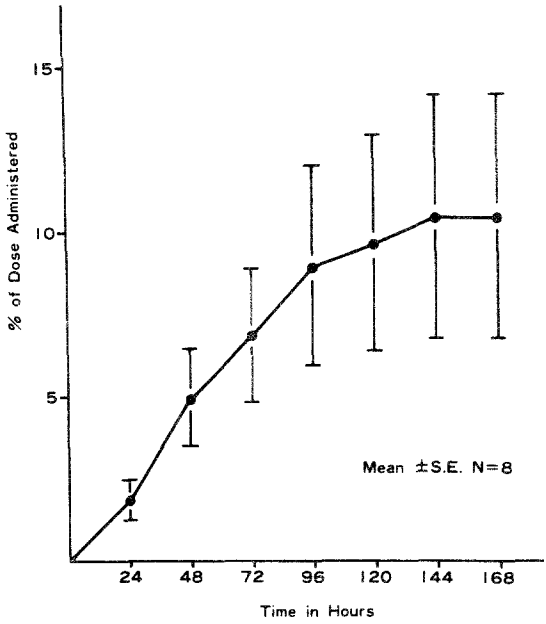

Fig. 4. Cumulative excretion of piroxicam as unchanged drug in urine. Data obtained from eight observations in seven subjects given either 30 mg ($n = 4$) or 60 mg ($n = 4$) piroxicam are expressed as the mean ±SEM percent of dose administered. One of seven subjects took two dose levels on two separate occasions 4 weeks apart.

variations of the absorption rate constant were large after an overnight fast, these values were also significantly different between the two groups ($p < 0.01$, Table II). It is therefore concluded that the rate of piroxicam absorption, but not its bioavailability, is significantly less when the drug is taken after food.

Side Effects and Hematology Values

The WBC in one subject was found to be reduced on the eighth day after a 60-mg dose. The lowest count was 2900/mm^3 on the sixteenth day. Other hematological values determined before the trial and on the sixteenth day after dosing were RBC, 471 and 449 ($\times 10^4$)/mm^3; Hb, 15.4 and 14.1 g%; Hct, 43.8% and 41.2%; platelets, 26.3 and 25.9 ($\times 10^4$)/mm^3. All hematological values (raw data available on request) examined in all individuals of group II remained entirely within the normal ranges during the follow-up period. Intra- and intersubject comparisons for all values were

Table II. Average Piroxicam Pharmacokinetic Parameters Obtained in Healthy Volunteers after Food (Group II)[a]

Parameters	n	Unit	Mean ± SEM	Significant difference from group I study (N.S., $p > 0.05$)
$t_{1/2}$	19	hr	32.9 ± 4.9	N.S.
k_{el}	19	day^{-1}	0.50 ± 0.06	N.S.
V_d/F	19	liters	8.12 ± 0.55	N.S.
		liter/kg	0.136 ± 0.009	N.S.
Total plasma clearance/F	19	ml/hr/kg	3.12 ± 0.16	N.S.
$[AUC]_0^\infty$ at 30-mg dose level	9	(μg/ml) × hr	189.9 ± 23.5	N.S.
$[AUC]_0^\infty$ at 60-mg dose level	10	(μg/ml) × hr	312.8 ± 22.3[b]	N.S.
C_{max} at 30-mg dose level	9	μg/ml	2.98 ± 0.23	$p < 0.01$
C_{max} at 60-mg dose level	10	μg/ml	6.39 ± 0.49[c]	N.S.
t_{max} observed	19	hr	4.3 ± 1.6	$p < 0.05$
predicted[d]	18[e]	hr	5.36 ± 0.38	$p < 0.001$
k_a	18[e]	hr^{-1}	0.80 ± 0.14	$p < 0.01$

[a] All data are expressed as mean ± SEM.
[b] $p < 0.002$ from 30-mg dose.
[c] $p < 0.001$, same as above.
[d] Calculated by equation 3.
[e] Insufficient data points for calculation in one subject.

found to be normal as compared both with each subject's own control value before drug administration and with values for those taking placebo.

DISCUSSION

Our observations indicate that piroxicam, a newly developed nonsteroidal anti-inflammatory drug, has an extended plasma half-life (approximately 1.4–1.6 day) in man. A double-blind study of patients with rheumatoid arthritis by Weintraub *et al.* (2) has recently shown that, on a once-daily dosing of 20 or 30 mg piroxicam, clinically and statistically significant improvement occurs in grip strength, walking time, and morning stiffness. These results together with the extended half-life observed in the present study imply that a single daily dose can permit the therapeutic concentrations to be maintained. The drug is largely metabolized, since only approximately 10% of an administered dose is excreted in the urine. The apparent volume of distribution (V_d/F) of piroxicam (approximately 7.5–9.5 liters or 0.12–0.14 liter/kg) is similar to that of other acidic and highly protein-bound anti-inflammatory drugs, such as fenoprofen (5) and tolmetin (13). This is similar to other drugs which do not easily penetrate cell membranes and are largely limited to the space occupied by plasma albumin and, therefore, mainly in the approximate space of the extracellular fluid

compartment (14). Since the half-life of a drug is expressed as $0.693 \times V_d$/metabolic clearance rate, the extended $t_{1/2}$ of this drug is largely due to the low clearance rate (approximately 3.5–4.6 liters/day).

A recent double-blind study of patients with active, definite rheumatoid arthritis by Weintraub *et al.* (2) has shown that the ranges of plasma piroxicam concentrations were 1.6–4.7 μg/ml (mean is calculated as 3.23 μg/ml), 8 weeks after a daily dose of 20 mg. According to Wagner *et al.* (15), a multiple dosing schedule can be predicted from single oral dose data, if certain pharmacokinetic parameters are known. For example, the average plasma concentration (C_{av}) of a drug in a steady state can be calculated using the absorbed fraction of the dose divided by $V_d \times k_{el} \times \tau$, where τ is the dosing interval. We generated the predicted plasma levels utilizing the whole mean of the pharmacokinetic data obtained in 27 observations as given in Table III. Assuming once-daily 20-mg dosing ($\tau = 1$ day), one can obtain a predicted plasma level range of 3.4–5.5 μg/ml with a mean steady-state concentration (C_{av}) of 4.3 μg/ml, which can be calculated by using the equation, $C_{av} = D/(V_d/F) \times k_{el} \times \tau$ as given in Table III. This seems to be fairly close to the mean value calculated from the data after 8 weeks of therapy by Weintraub *et al.* (2). However, whether or not our data obtained from normal individuals after a single oral dose can be directly translated to patients requiring treatment with an anti-inflammatory drug such as piroxicam clearly needs further investigation in patients. Rheumatic disease presents a complex clinical course (16) which can affect drug kinetics; hypoalbuminemia and other pathophysiological changes often occur, and drug interactions can influence drug kinetics in patients given two or more drugs simultaneously. The prediction of steady-state plasma levels from single-dose data in normal volunteers will therefore have certain limitations (15).

Table III. Summarized Data of Piroxicam Pharmacokinetics Obtained in 27 Observations and Predicted Steady-State Plasma Levels

Parameters	Unit	Mean ± SEM
$t_{1/2}$	hr	34.26 ± 3.54
k_{el}	day^{-1}	0.48 ± 0.05
V_d/F	liter/kg	0.137 ± 0.007
Total plasma clearance/F	ml/hr/kg	2.94 ± 0.14
Predicted steady-state plasma levels[a] for a 20-mg once-daily dose in a 70-kg man		
C_{max}	μg/ml	5.5
C_{av}	μg/ml	4.3
C_{min}	μg/ml	3.4

[a] The following equations were used: $C_{max} = [\text{dose}/(V_d/F)](1 - e^{-k_{el}\tau})$, $C_{av} = \text{dose}\ (V_d/F) \times k_{el} \times \tau$, and $C_{min} = [\text{dose} \times e^{-k_{el}} \times \tau/(V_d/F)](1 - e^{-k_{el}\tau})$.

We observed that food intake can have a significant influence on both the absorption rate constant and the time at which peak levels of this drug are achieved, despite the fact that there is no significant difference between AUC values in the fasting state and after food. The value of C_{max} after a 30-mg dose, but not a 60-mg dose, in the fasting state was significantly greater than in the nonfasting state. Schumacher (17) has pointed out that C_{max} values can usually be employed as a relative index of AUC, and therefore bioavailability, only when (a) t_{max} values are approximately equal for the various dosage forms examined, (b) $k_a \gg k_{el}$, and (c) average k_{el} and V_d values remain constant for the sample and reference study group. Our absorption data indicate that only t_{max} values did not support this concept. On the other hand, an increase in t_{max} values usually suggests a decrease in k_a, but it does not necessarily reflect a decrease in AUC values. This was the case in our study. A recent review (18) concerning the influence of food on drug absorption has indicated that the absorption of drugs from the gastrointestinal tract is generally reduced or delayed by food intake. The observed effects of food on drug absorption are the net result of various factors, including the influence of food on gastrointestinal physiology and physicochemical interactions of drugs, drug dosage forms, the dietary components. However, since the anti-inflammatory drugs such as piroxicam are usually given in multiple doses and the AUC is not greatly affected by food intake, the changes in two absorption parameters k_a and t_{max} are not considered clinically important, unless the drug is indicated for acute pain or fever.

In the present study, one subject in group I showed a reduced WBC, which was found to be below the normal range on days 8 and 16 after the 60-mg dose. The reason for this finding is not clear from the present study. No subject in group II was found to have abnormal hematology when the initial control values were compared with the postdrug values or the pre- and postdrug values found in ten normal, healthy individuals taking placebo alone. Nevertheless, close observation is warranted in large-scale trials with piroxicam because some drugs of this class are known to cause hematological changes (19).

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