Single- and Multiple-Dose Pharmacokinetics of Etoricoxib, a Selective Inhibitor of Cyclooxygenase-2, in Man

Nancy G. B. Agrawal, PhD, Arturo G. Porras, PhD, Catherine Z. Matthews, BS, Mark J. Rose, PhD, Eric J. Woolf, PhD, Bret J. Musser, PhD, Andrea L. Dynder, MS, Katherine E. Mazina, MS, Kenneth C. Lasseter, MD, Thomas L. Hunt, MD, Jules I. Schwartz, PharmD, MPH, Jacqueline B. McCrea, PharmD, and Keith M. Gottesdiener, MD

The single- and multiple-dose pharmacokinetics of etoricoxib, a selective inhibitor of cyclooxygenase-2, were examined in two clinical studies. Single-dose pharmacokinetics—including dose proportionality, absolute bioavailability of the highest dose-strength (120-mg) tablet, and the effect of a high-fat meal on the bioavailability of that tablet—were investigated in a two-part, open, balanced crossover study in two panels of healthy subjects (12 per panel). Steady-state pharmacokinetics were investigated in an open-label study in which 24 healthy subjects were administered 120-mg single and multiple (once daily for 10 days) oral doses of etoricoxib tablets. The pharmacokinetics of etoricoxib were found to be consistent with linearity through doses at least twofold greater than the highest anticipated clinical dose of 120 mg. Etoricoxib administered as a tablet was rapidly and completely absorbed and available; the absolute bioavailability was estimated to be 100%. A high-fat meal decreased the rate of absorption without affecting the extent of absorption of etoricoxib; therefore, etoricoxib can be dosed irrespective of food. Steady-state pharmacokinetics of etoricoxib, achieved following 7 days of once-daily dosing, were found to be reasonably predicted from single doses. The accumulation ratio averaged 2.1, and the corresponding accumulation $t_{1/2}$ averaged 22 hours, supporting once-daily dosing. Etoricoxib was generally well tolerated.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in clinical practice for the treatment of pain, inflammation, and fever. The pharmacological effects of these drugs are due to their ability to block prostaglandin synthesis by inhibiting the enzyme cyclooxygenase (COX).[1-5] COX exists in two isoforms in man: COX-1 and COX-2. COX-1 is constitutively expressed in healthy tissues and mediates the production of prostaglandins required for many physiologic "housekeeping" functions, such as protection of the gastric mucosa, maintenance of renal homeostasis, and platelet aggregation. Conversely, COX-2 is inducible in response to inflammatory or mitogenic stimuli in many tissues, and its expression has been hypothesized to be responsible for the synthesis of prostaglandins which mediate responses to pathologic processes such as pain, fever, and inflammation. The analgesic, anti-inflammatory, and antipyretic effects of all NSAIDs are believed to arise primarily through inhibition of COX-2, whereas the reduced gastric mucosal protection associated with nonselective NSAIDs, which inhibit both COX-1 and COX-2, is thought to arise from inhibition of COX-1. Thus, agents that selectively inhibit COX-2 can be expected to be as clinically effective as nonselective NSAIDs in the treatment of ar-

From Merck Research Laboratories, West Point, Pennsylvania (Dr. Agrawal, Dr. Porras, Ms. Matthews, Dr. Rose, Dr. Woolf); Merck Research Laboratories, Rahway, New Jersey (Dr. Musser, Ms. Dynder, Ms. Mazina, Dr. Schwartz, Dr. Gottesdiener); Merck Research Laboratories, Blue Bell, Pennsylvania (Dr. McCrea); Clinical Pharmacology Associates, Miami, Florida (Dr. Lasseter); and PPD Development, Inc., Austin, Texas (Dr. Hunt).
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thritis, pain, and associated conditions but with a much reduced risk of gastrointestinal toxicity.[1,3,4,6,7]

Etoricoxib (5-chloro-6'-methyl-3-[4-(methylsulfonyl) phenyl]-2,3'-bipyridine) is a selective inhibitor of COX-2 that has been developed for the treatment of osteoarthritis, rheumatoid arthritis, and pain.[8] The single- and multiple-dose pharmacokinetics of etoricoxib in healthy subjects—including the absolute bioavailability of the highest dose-strength tablet, the effect of a high-fat meal on the bioavailability of the tablet, and dose proportionality over the dose range of 30 to 240 mg—were examined in the two studies described here.

METHODS

Study Designs

Single-Dose Study (Bioavailability/ Food Effect/Dose Proportionality)

To evaluate the absolute bioavailability of the highest dose-strength (120-mg) tablet of etoricoxib, the effect of a high-fat meal on the bioavailability of the tablet, and the dose proportionality of etoricoxib, a two-part, open, balanced crossover study was conducted in two panels of healthy subjects. In part I, to assess the absolute bioavailability of the highest dose-strength tablet and the effect of a high-fat meal on the bioavailability of the tablet, a panel of 12 subjects (mean age: 57 years; range: 50-64 years; 6 men, 6 women) was administered single 120-mg oral doses of etoricoxib (1 × 120-mg tablet) in the fasted state and after a high-fat meal and a single 25-mg intravenous (IV) dose in an open, three-period, randomized, balanced crossover fashion. The IV dose was administered as a citrate-buffered saline solution by 15-minute infusion (33 mL). Actual weights of IV solution administered were recorded for each subject. In part II, to examine the dose proportionality of etoricoxib, a second panel of 12 subjects (mean age: 53 years; range: 43-65 years; 6 men, 6 women) was administered single oral doses of 30, 60, 120, and 240 mg (2 × 120-mg tablet) etoricoxib in an open, four-period, randomized crossover fashion. The different dose-strength tablets administered were proportionally formulated and contained 20% active ingredient by weight. At least a 10-day washout period was required between etoricoxib doses in each part of the study. All oral doses were administered with 240 mL of water after an overnight fast, with the exception of the period in part I in which the 120-mg tablet was administered within 5 minutes after consuming a high-fat breakfast (2 eggs, 2 strips of bacon, 2 slices of white toast, 2 to 4 ounces of hash brown potatoes, and 250 mL of whole milk). Standard meals were provided for all subjects through the first 36 hours of each study period. Blood samples were collected in heparinized tubes at predose and 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 15, 18, 24, 30, 36, 48, 60, 72, 96, and 120 hours following each dose. Additional blood samples were collected at 0.25 and 0.75 hours following the IV dose. The blood samples were protected from light and stored on ice until the plasma could be separated. The separated plasma was stored at –20°C until analysis for etoricoxib.

Multiple-Dose Study

To investigate the steady-state pharmacokinetics of etoricoxib, an open-label study was conducted in which 24 healthy subjects (mean age: 36 years; range: 25-50 years; 12 men, 12 women) were administered 120-mg single and multiple oral doses (120 mg once daily for 10 days) of etoricoxib. An 8-day washout period was required between the single dose and the start of multiple dosing. Doses were administered with 240 mL of water. The single dose and the last dose of multiple dosing were administered after at least a 10-hour fast. Standard meals were provided for all subjects through the first 36 hours following both the single and last doses. Blood samples were collected in heparinized tubes at predose and at 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 15, 18, 24, 30, 36, 48, 60, 72, 96, and 120 hours following the single dose and the last dose of multiple dosing. Blood samples were also collected at predose on each dosing day during multiple dosing and at 168 hours following the last dose of multiple dosing. The blood samples were protected from light and stored on ice until the plasma could be separated. The separated plasma was stored at –20°C until analysis for etoricoxib.

For both studies described here, all subjects were within 30% of ideal body weight and were in good health according to routine medical history, physical examination, and laboratory data (hematology, blood chemistry, and urinalysis). Women of childbearing potential were required to have a negative pregnancy test and to use appropriate barrier contraception during the study. Subjects were required to refrain from consumption of grapefruit juice, herbal remedies, and nonstudy drugs/medications for 2 weeks prior to and throughout the study. Subjects were excluded if they had a history of cardiac or vascular disorder, other pulmonary disease, major gastrointestinal (GI) abnormalities/peptic ulceration, or hepatic, neurologic, endocrine, renal, or major genitourinary disease. Subjects were also excluded if they had a history of serious adverse experiences related to NSAID use; had documented drug al-

lergies or were allergic or intolerant to aspirin, ibuprofen, or other NSAIDs or COX-2 inhibitors; or had a history of asthma and nasal polyps associated with aspirin or NSAIDs. The subjects provided written informed consent and agreed to follow study procedures. Each study was approved by the appropriate institutional review board/ethical review committee and conformed with the Declaration of Helsinki as written at the time of study initiation. The single-dose study was conducted at Clinical Pharmacology Associates (Miami, FL), and the protocol was reviewed and approved by Southern Institutional Review Board, Inc. The multiple-dose study was conducted at PPD Development, Inc. (Austin, TX), and the protocol was reviewed and approved by Research Consultants Review Committee.

Analytical Methods

Plasma samples collected following each dose were assayed for etoricoxib by the method of Matthews et al.[9] Analysis was accomplished by solid-phase extraction of the analyte and an internal standard from plasma using a 96-well plate format followed by reverse-phase HPLC in a system equipped with a postcolumn photochemical reactor and a fluorescence detector.

The standard curve analyzed daily with clinical samples ranged from 5 to 500 ng/mL. Intraday accuracy determined by replicate (n = 5) analysis of standards ranged from 94% to 107%. Intraday precision (expressed as percent coefficient of variation) was < 8%, as assessed by replicate analysis of standards. As assessed by coefficients of variation of low-, medium-, and high-quality control samples, interday precision was < 5%.

Pharmacokinetic Methods

For both studies described here, actual sampling times relative to drug administration were used to estimate pharmacokinetic parameters.

The terminal half-life ($t_{1/2}$) was estimated from the best-fit parameters of a single exponential to the log-linear portion of the plasma concentration-time curve. The best-fit parameters were obtained using nonlinear regression by the Simplex algorithm, with weight = 1.[10] Following single oral and IV doses, the area under the plasma concentration-time curve (AUC_∞) was calculated using the linear trapezoidal method up to the last measured concentration, and the remaining area was extrapolated from the ratio of that concentration and the value of ln (2)/terminal $t_{1/2}$ estimated for that administration. The maximum concentration observed in plasma (C_{max}) and its time of occurrence (t_{max}) following oral doses were obtained by inspection of the concentration-time data.

Following IV administration, the area under the first moment curve (AUMC) was calculated using the linear trapezoidal method and the appropriate extrapolations. Plasma clearance (CL) was calculated as the ratio of dose to AUC_∞. For each individual, the actual IV dose administered was used, where actual dose = (weight of dosing solution administered) ÷ (formulation density) × (assayed potency of the dosing solution administered). The steady-state volume of distribution (V_{dss}) was calculated as

$$V_{dss} = CL \bullet MRT = \frac{Dose_{IV}}{AUC_\infty}\left[\frac{AUMC}{AUC_\infty} - \frac{\tau_{inf}}{2}\right],$$

where MRT is the mean residence time and τ_{inf} is the infusion time (0.25 h).

Absolute bioavailability following single oral doses was assessed by dose-adjusted AUC_∞ ratios (oral/IV), where the actual IV and oral doses administered, adjusted for assayed potencies of the formulations, were used.

Following multiple oral dosing, the AUC during a dosing interval (AUC_{24h}) was calculated using the linear trapezoidal method. The accumulation ratio (R) was calculated from the ratio of AUC_{24h} values following the last dose to the first dose. The accumulation $t_{1/2}$ was calculated from R, where

$$R = \frac{1}{1 - e^{-k\tau}},$$

and k = ln (2)/accumulation $t_{1/2}$, and τ is the dosing interval (24 h).

For the few cases in the single-dose study in which the washout interval between treatment periods was insufficient, as evidenced by the presence of measurable concentrations in predose plasma samples, the contributions to the observed plasma concentrations from the previous dose were estimated assuming exponential decay of the concentration observed at t = 0 using the terminal $t_{1/2}$ estimated for that administration. Prior to determination of AUC_∞ and C_{max} values, the plasma profiles were corrected by subtracting the estimated contribution of the previous dose.

To facilitate comparisons of pharmacokinetic data across studies and to correct for differences in the measured drug content of the different formulations used in the studies, all AUC_∞ and C_{max} values were adjusted for assayed potencies of the formulations.

Statistical Methods

Single-Dose Study (Absolute Bioavailability/Food Effect/ Dose Proportionality)

The absolute bioavailability of the 120-mg tablet and the effect of a high-fat meal on etoricoxib pharmacokinetics were assessed using an analysis of variance (ANOVA) model for a three-period crossover design, with factors for treatment, subject, and period. Carryover was tested in the ANOVA model but was not included in the final model because it was not found to be significant. Inspection of the residuals revealed no departures from homogeneous variance or normality. The gender-by-treatment interaction was tested but not found to be significant. The absolute bioavailability of the 120-mg tablet was estimated by the geometric mean ratio (GMR) (fasted oral treatment/IV treatment) of the dose-normalized (to 1 mg), log-transformed AUC_∞ values. The difference between the least squares means for the oral and IV treatments and the corresponding standard error for the difference were used to calculate the 95% confidence interval (CI) for the treatment difference on the log scale. All results were back-transformed from the log scale. The effect of a high-fat meal on etoricoxib pharmacokinetics was estimated by the GMR (fed oral treatment/fasted oral treatment) of log-transformed AUC_∞ and C_{max} values. The AUC GMR and 90% CI were calculated using the ANOVA model described above. Log-transformed C_{max} values were analyzed using an ANOVA model with the terms sequence, subject within sequence, period, and treatment (fed or fasted). The CI for C_{max} was constructed with the *t*-distribution using the variance estimate from the ANOVA model.

Dose proportionality was assessed by the combination of a pairwise comparison approach and the power law model.[11] First, an ANOVA model with terms for sequence, subject within sequence, period, and dose (3 degrees of freedom) was used to analyze dose-normalized (to 1 mg), log-transformed AUC_∞ and C_{max} data. Carryover was marginally significant for AUC_∞ and significant for C_{max}. Since the design was balanced to estimate carryover, carryover was included in the ANOVA model and least squares means were determined. The standard model assumptions of normality and homogeneous variance were assessed by an examination of the results and found to generally hold. Second, the pairwise comparison at the highest to lowest dose (240 mg/30 mg) was calculated for AUC_∞ and C_{max} to assess any potential nonlinearity at the highest dose. Also, 90% CIs for the pairwise comparisons between doses were generated from the ANOVA model, based on the *t*-distribution. Third, for the power law model, log-transformed AUC_∞ data were modeled as a function of subject, period, and log-transformed dose (as a 1 degree-of-freedom covariate). Linearity was tested by adding a quadratic term for log-transformed dose, which was found to be nonsignificant. The 90% CI for the slope of log-transformed AUC_∞ versus log-transformed dose was computed from the linear regression model. To supplement the above analysis, a plot was prepared of the AUC_∞ and C_{max} data versus dose with the regression line from the analysis of covariance (ANCOVA) model, including all doses. The regression line and corresponding 90% confidence bands provide a visual aid in assessing dose proportionality.

All AUC_∞ and C_{max} values were adjusted for assayed potencies of the formulations and were log-transformed prior to statistical analysis. The parameters t_{max} and apparent terminal $t_{1/2}$ were summarized for the oral treatments (fed and fasted). The t_{max} values were rank-transformed, and apparent terminal $t_{1/2}$ values were inverse-transformed. Clearance, $t_{1/2}$, and V_{dss} were summarized for the IV treatment. Clearance values were log-transformed, $t_{1/2}$ values were inverse-transformed, and V_{dss} values were analyzed on the original scale. All results were back-transformed (as necessary) to the original scale for presentation.

Multiple-Dose Study

Attainment of steady state was assessed by analyzing log-transformed trough concentrations (predose on multiple dose days 2-10) using appropriate orthogonal linear contrasts and curvature contrasts (using the quadratic contrast). The ANOVA model contained factors for subject and day. Starting with multiple-dose day 2 in a step-up procedure, the contrasts for the linear and quadratic (for curvature purposes) terms were examined for statistical significance. If either of the above contrasts was significant, then the analyses proceeded to multiple-dose day 3 with new linear and quadratic contrasts computed. The procedure was continued throughout the time course until both contrasts were nonsignificant. At the point of nonsignificance of the linear and quadratic terms, the approximate day of attainment of steady state was declared.

The pharmacokinetic parameters AUC_{24h}, C_{max}, t_{max}, and apparent terminal $t_{1/2}$ were compared between single doses and the last dose of multiple dosing using a paired *t*-test. Each parameter was transformed as part of satisfying the assumptions for the test: AUC_{24h} and C_{max} were log-transformed, $t_{1/2}$ was inverse-transformed, and t_{max} was ranked. The normality assumption was

tested using the Shapiro-Wilk's statistic. Slight nonnormality due to outliers was detected for C_{max}, but the value of the statistic (W = 0.896) demonstrated that the data did not deviate too greatly from this assumption. The parameters AUC_{∞} (following single-dose administration), accumulation ratio, and accumulation $t_{1/2}$ were also summarized. AUC_{∞} values and accumulation ratios were log-transformed, and accumulation $t_{1/2}$ values were inverse-transformed. All AUC and C_{max} values were adjusted for assayed potencies of the formulations prior to statistical analysis.

To determine whether multiple-dose pharmacokinetic behavior is predicted by single-dose pharmacokinetics, the GMR of steady-state AUC ($AUC_{24h,\ Last\ Dose}$)/single-dose AUC_{∞} was calculated (performed on the log scale and back-transformed for reporting) and compared to 1.0. It was prespecified that if the 90% CI for the GMR was within the interval (0.70, 1.43), then no clinically meaningful difference between single-dose AUC_{∞} and $AUC_{24h,\ Last\ Dose}$ would be concluded.

Assessments of Safety and Tolerability

Vital signs, physical examination, routine hematology, blood chemistry, urinalysis, and ECGs were monitored prestudy and poststudy. Adverse experiences were evaluated by the investigator as to their intensity, seriousness, and relationship to study drug.

RESULTS

Pharmacokinetics

Intravenous Pharmacokinetics and Absolute Bioavailability of the 120-mg Tablet

Concentrations of etoricoxib in plasma decline in approximately a biphasic manner following single 25-mg IV doses, as shown in Figure 1. Minor secondary peaks are evident in the individual plasma concentration-time profiles; the origin of these minor secondary peaks is unknown.

Summary statistics of pharmacokinetic parameter values following single IV doses as well as the bioavailability of the 120-mg tablet are listed in Table I. The systemic clearance of etoricoxib is relatively low (49 mL/min), and the steady-state volume of distribution is large (119 L), resulting in a relatively long terminal half-life (~27 h). The absolute bioavailability of the 120-mg tablet was estimated to average 101%, with a 95% CI of (93%, 111%).

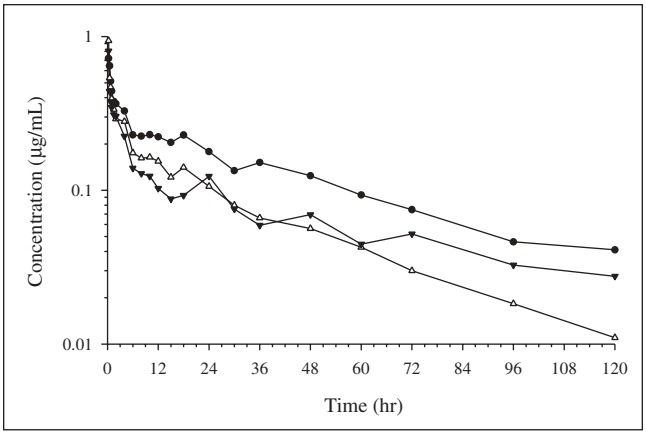

Figure 1. Representative individual concentration-time profiles of etoricoxib in plasma of healthy subjects following administration of 25-mg single IV doses.

Table I Summary Statistics of Pharmacokinetic Parameter Values for Etoricoxib following Administration of 25-mg Single IV Doses to 12 Healthy Subjects and Bioavailability of the 120-mg Tablet

Parameter	Mean (*SD*)	
Clearance (mL/min)[a]	49	(23)
V_{dss} (L)[b]	119	(37)
$t_{1/2}$ (h)[c]	27.3	(18.2)
Bioavailability (%)[d]	101	(93, 111)

a. Geometric mean (between-subject *SD*).
b. Arithmetic mean (*SD*).
c. Harmonic mean (jackknife *SD*).
d. Geometric mean (95% confidence interval).

Food Effect

Mean concentrations of etoricoxib in plasma following administration of single 120-mg oral doses in the fasted state and after a high-fat meal are shown in Figure 2. Minor secondary peaks are evident in both the individual and mean plasma concentration-time profiles, consistent with those seen following single IV doses (Figure 1). Summary statistics of pharmacokinetic parameter values in the fasted and fed states are listed in Table II.

A high-fat meal had no effect on the extent of absorption of etoricoxib, although it did decrease the rate of

Table II Summary Statistics of Pharmacokinetic Parameter Values for Etoricoxib following Administration of 120-mg Single Oral Doses to 12 Healthy Subjects under Fasted Conditions and after a High-Fat Meal

Treatment	AUC_∞ (μg•h/mL)[a]	C_{max} (μg/mL)[a]	t_{max} (h)[b]	Apparent Terminal $t_{1/2}$ (h)[c]
Fasted	41.35 (23.28)	2.43 (0.66)	1.0 (0.5, 2.0)	28.7 (15.9)
Fed	40.16 (18.28)	1.56 (0.36)	3.0 (0.5, 10.0)	27.6 (15.1)
Geometric mean ratio (fed/fasted) (90% confidence interval)	0.97 (0.90, 1.05)	0.64 (0.53, 0.78)	—	—

— = not calculated.
a. Geometric mean (between-subject *SD*), back-transformed from the log scale.
b. Median (minimum, maximum).
c. Harmonic mean (jackknife *SD*).

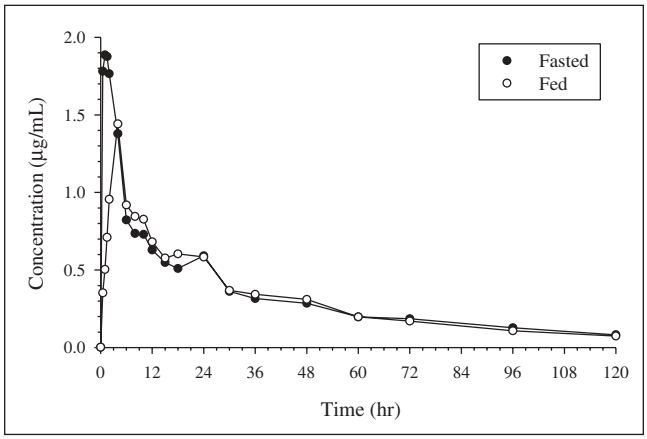

Figure 2. Mean concentration-time profiles of etoricoxib in plasma of 12 healthy subjects following administration of 120-mg single oral doses in the fasted state and after a high-fat meal.

absorption. The fed/fasted GMRs (90% CI) for AUC_∞ and C_{max} were 0.97 (0.90, 1.05) and 0.64 (0.53, 0.78), respectively. When etoricoxib was administered after a high-fat meal, t_{max} was delayed by approximately 2 hours. Apparent terminal $t_{1/2}$ values were not significantly different between the fed and fasted treatments ($p > 0.200$).

Dose Proportionality

Mean concentrations of etoricoxib in plasma following administration of 30-, 60-, 120-, and 240-mg single oral doses are shown in Figure 3. Summary statistics of pharmacokinetic parameter values between doses are listed in Table III.

Geometric least squares mean AUC_∞ values normalized to a 1-mg dose were 0.30, 0.31, 0.30, and 0.32 μg•h/mL/mg for the 30-, 60-, 120-, and 240-mg doses, respectively. In the ANOVA model using normalized AUC_∞ as the response, no statistically significant differences were observed between the doses.

Geometric mean AUC_∞ values are shown plotted versus dose in Figure 4, along with the regression line and its 90% confidence band. The slope of the regression line for AUC_∞ was 1.01, and the 90% CI was (0.99, 1.04). The AUC_∞ GMR at the highest to lowest dose (240 mg/30 mg) was 1.06, and the 90% CI was (1.00, 1.12); the GMR was not significantly different from 1.0 ($p = 0.116$). These results are consistent with dose proportionality of etoricoxib AUC_∞ across the 30- to 240-mg dose range.

Geometric least squares mean C_{max} values normalized to a 1-mg dose were 18, 21, 18, and 18 ng/mL/mg for the 30-, 60-, 120-, and 240-mg doses, respectively. In the ANOVA model using normalized C_{max} as the response, the overall effect of dose was statistically significant ($p = 0.028$); however, no trend with dose was apparent.

Geometric mean C_{max} values are shown plotted versus dose in Figure 4, along with the regression line and its 90% confidence band. The slope of the regression line for C_{max} was 0.99, and the 90% CI was (0.92, 1.05). The C_{max} GMR at the highest to lowest dose (240 mg/30 mg) was 1.05, and the 90% CI was (0.93, 1.19); the GMR did not differ significantly from 1.0 ($p > 0.200$). These results are consistent with dose proportionality of etoricoxib C_{max} across the 30- to 240-mg dose range.

Median t_{max} values were 1.8, 1.0, 1.5, and 1.3 hours for the 30-, 60-, 120-, and 240-mg doses, respectively. Although small but significant differences among doses were observed ($p = 0.005$), there was no apparent dose-dependent trend.

The harmonic mean apparent terminal $t_{1/2}$ values averaged approximately 29 hours, and no statistically significant differences were observed across the doses ($p > 0.200$).

Table III Summary Statistics of Pharmacokinetic Parameter Values for Etoricoxib following Administration of Single Oral Doses of Etoricoxib to 12 Healthy Subjects

Dose (mg)	AUC_∞ (μg•h/mL)[a]		C_{max} (μg/mL)[a]		t_{max} (h)[b]		Apparent Terminal $t_{1/2}$ (h)[c]	
30	9.08	(3.39)	0.53	(0.14)	1.8	(0.5, 4.0)	28.5	(10.6)
60	18.57	(7.29)	1.27	(0.36)	1.0	(0.5, 1.5)	29.9	(7.3)
120	35.84	(15.05)	2.14	(0.60)	1.5	(0.5, 2.0)	28.4	(9.8)
240	76.10	(33.76)	4.37	(1.20)	1.3	(0.5, 2.0)	27.6	(9.6)

a. Geometric mean (between-subject *SD*), back-transformed from the log scale.
b. Median (minimum, maximum).
c. Harmonic mean (jackknife *SD*).

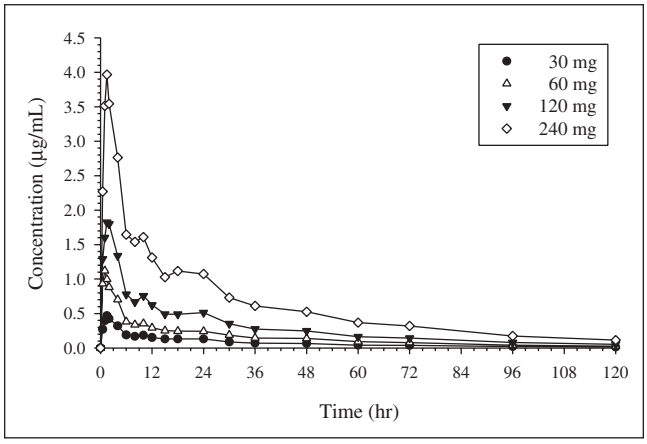

Figure 3. Mean concentration-time profiles of etoricoxib in plasma of 12 healthy subjects following administration of single oral doses of 30, 60, 120, and 240 mg etoricoxib.

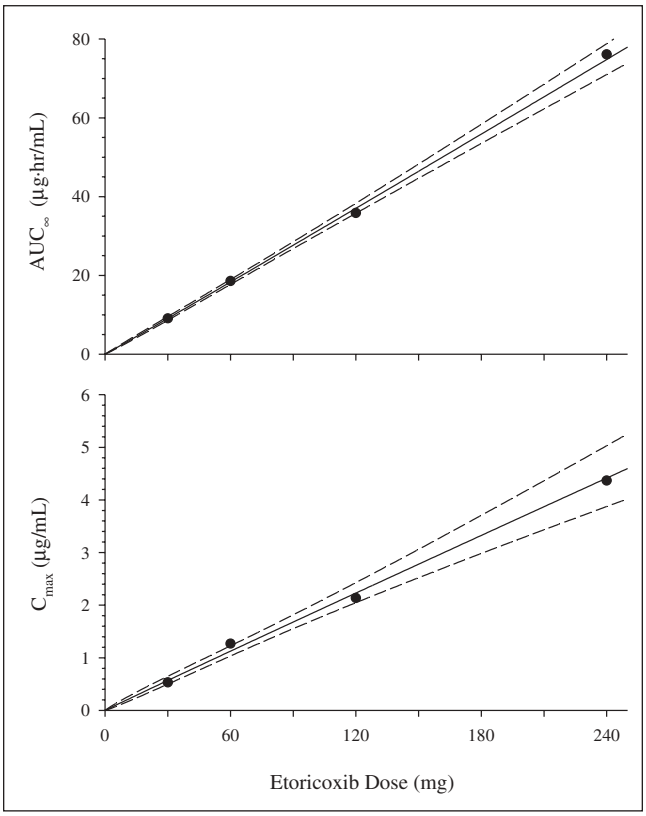

Figure 4. Dependence of AUC_∞ and C_{max} on etoricoxib dose (with regression line and 90% confidence bands) following administration of single oral doses of etoricoxib to 12 healthy subjects.

Multiple-Dose Pharmacokinetics

Mean concentrations of etoricoxib in plasma following administration of 120-mg single and multiple oral doses are shown in Figure 5. The mean plasma concentrations are plotted for 24 hours after the single dose, before drug administration on multiple dose days 3 to 9, and for 168 hours after the last (10th) daily dose. Summary statistics of pharmacokinetic parameter values following administration of single and multiple doses are listed in Table IV.

Analysis of trough concentrations suggests that steady state was achieved following approximately 7 days of once-daily dosing. The accumulation ratio based on AUCs averaged 2.1, which corresponds to an accumulation $t_{1/2}$ of approximately 22 hours. The ratio of steady-state AUC_{24h} to single-dose AUC_∞ averaged 1.11, with a 90% CI of (1.04, 1.18), which fell within the prespecified interval of (0.70, 1.43). The GMR was found to be significantly different from 1.0 ($p = 0.010$), but the deviation is small and not clinically relevant. Taken together, these results are generally consistent with linearity of etoricoxib pharmacokinetics and the time invariance of clearance.

Table IV Summary Statistics of Pharmacokinetic Parameter Values for Etoricoxib following Administration of 120-mg Single and Multiple Oral Doses to 24 Healthy Subjects

Parameter	Single Dose				Last Dose	
AUC_{24h} (μg•h/mL)[a]	18.43	(4.56)			37.83	(16.51)
AUC_{∞} (μg•h/mL)[a]	34.18	(16.93)			—	
C_{max} (μg/mL)[a]	2.05	(0.67)			3.59	(1.31)
t_{max} (h)[b]	1.5	(0.5, 24.0)			1.3	(0.5, 4.0)
Apparent terminal $t_{1/2}$ (h)[c]	23.8	(8.6)			25.2	(8.7)
Accumulation ratio[d]			2.05	(1.85, 2.28)		
Accumulation $t_{1/2}$ (h)[c]			22.3	(9.1)		
$AUC_{24h,\ Last\ Dose}/AUC_{\infty}$[d]			1.11	(1.04, 1.18)		

— = not calculated.
a. Geometric mean (between-subject *SD*), back-transformed from the log scale.
b. Median (minimum, maximum).
c. Harmonic mean (jackknife *SD*).
d. Geometric mean (90% confidence interval), back-transformed from the log scale.

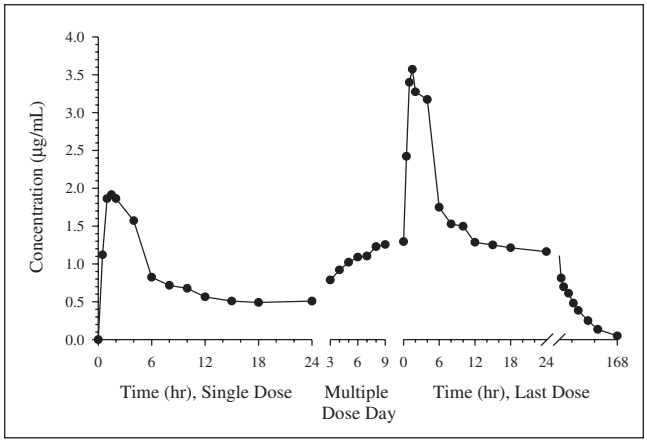

Figure 5. Mean concentration-time profile of etoricoxib in plasma of 24 healthy subjects following administration of a single 120-mg oral dose and 120-mg oral doses once daily for 10 days.

Safety and Tolerability

Etoricoxib was generally well tolerated in both studies. In the single-dose study, 4 of the 24 subjects had five clinical adverse experiences that were judged to be possibly or probably drug related. Two of these (dizziness and fatigue) occurred at the 120-mg dose (with food), and three (headache and two episodes of diarrhea) occurred at the 30-mg dose. No clinical adverse experience was serious, and no subject discontinued due to a clinical adverse experience. No laboratory adverse experiences were reported.

In the multiple-dose study, 12 of 24 subjects had 19 clinical adverse experiences that were judged to be possibly or probably drug related. These clinical adverse experiences included 8 instances of taste disturbance, 3 instances of headache, 2 instances of nausea, and 1 instance each of decreased appetite, dizziness, flatulence, increased thirst, insomnia, and darker yellow urine. All clinical adverse experiences were mild in intensity and all resolved. No serious adverse experience occurred. No laboratory adverse experiences were reported, and no subject discontinued due to an adverse experience.

DISCUSSION

Following single oral doses, the kinetics of etoricoxib appear to be linear over the entire dose range examined, from 30 to 240 mg. AUC_{∞} and C_{max} values increase proportionally with dose over this dose range (Figure 4). In further support of linearity, t_{max} and apparent terminal $t_{1/2}$ values are independent of dose. These results are consistent with those from a previous study in which dose proportionality was established at doses from 5 to 120 mg.[12] Together, these results support the position that the kinetics of etoricoxib are linear through single doses at least twofold greater than the highest anticipated clinical dose of 120 mg. Evidence from an early single-dose safety and tolerability study (not a definitive dose proportionality study) conducted in two panels of young subjects suggests that the pharmacokinetics of etoricoxib are also consistent with linearity through single doses up to at least 500 mg.[13]

Etoricoxib was found to be essentially completely absorbed and available following administration of the highest dose-strength tablet; the absolute bioavailability was estimated to be approximately 100%. Absorption of etoricoxib also appears to be

rapid, with t_{max} occurring at approximately 1 hour. Because the kinetics of etoricoxib are linear across a wide dose range and the different dose-strength tablets of etoricoxib (60, 90, and 120 mg) are proportionally formulated, it can be inferred that all lower dose-strength tablets are also completely absorbed and available.

A high-fat meal was found to have no effect on the extent of absorption of the 120-mg tablet of etoricoxib, although it did decrease the rate of absorption. AUC_∞ values were unaffected, as might be expected based on the 100% bioavailability of etoricoxib, whereas the C_{max} values were 36% lower and occurred 2 hours later when etoricoxib was administered following a high-fat meal. These results are consistent with a high-fat meal decreasing the rate of absorption of etoricoxib by delaying gastric emptying. Overall, these results support that etoricoxib can be dosed without regard to food intake since the observed differences are not expected to be of any clinical significance.

Analysis of the trough concentrations shows that steady state was achieved following approximately 7 days of once-daily dosing (Figure 5), as would generally be expected from apparent terminal half-life estimates following the single-dose portion of the multiple-dose study (~24 h) and following the last dose of multiple dosing (~25 h). The accumulation ratio averaged approximately 2.1. The corresponding accumulation $t_{1/2}$ of 22 hours, which is generally consistent with apparent terminal half-life estimates following single doses and the last dose of multiple dosing, supports a once-daily dosing regimen.

Steady-state pharmacokinetic behavior of etoricoxib was found to be reasonably well predicted from single-dose pharmacokinetic behavior. The GMR of steady-state AUC_{24h} to single-dose AUC_∞ averaged 1.11, and the 90% CI of (1.04, 1.18) fell within the prespecified interval of (0.70, 1.43). Although the GMR was significantly different from 1.0, the deviation is small and not clinically relevant. Taken together, these results support the linearity of etoricoxib pharmacokinetics and the time invariance of clearance.

Together, the predictability of steady-state pharmacokinetics from single 120-mg oral doses and the dose proportionality of AUC_∞ and C_{max} values following single oral doses from 5 to 240 mg (and most likely through at least 500 mg) are consistent with linear kinetics of etoricoxib.

Etoricoxib was generally well tolerated in both the single- and multiple-dose studies. The clinical adverse experiences that were considered to be possibly or probably drug related were all mild in intensity and resolved. These included dizziness, fatigue, headache, diarrhea, flatulence, increased thirst, insomnia, darker yellow urine, taste disturbance, nausea, and decreased appetite. There were no laboratory adverse experiences, and no serious adverse experiences were reported.

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