

## ABSORPTION, METABOLISM, AND EXCRETION OF ETORICOXIB, A POTENT AND SELECTIVE CYCLOOXYGENASE-2 INHIBITOR, IN HEALTHY MALE VOLUNTEERS

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### ABSTRACT:

[<sup>14</sup>C]Etoricoxib (100 μCi/dose) was administered to six healthy male subjects (i.v., 25 mg; p.o., 100 mg). Following the i.v. dose, the plasma clearance was 57 ml/min, and the harmonic mean half-life was 24.8 h. Etoricoxib accounted for the majority of the radioactivity (~75%) present in plasma following both i.v. and p.o. doses. The oral dose, administered as a solution in polyethylene glycol-400, was well absorbed (absolute bioavailability of ~83%). Total recovery of radioactivity in the excreta was 90% (i.v.) and 80% (p.o.), with 70% (i.v.) and 60% (p.o.) excreted in urine and 20% in feces after either route of administration. Radiochromatographic analysis of the excreta revealed that etoricoxib was metabolized

extensively, and only a minor fraction of the dose (<1%) was excreted unchanged. Radiochromatograms of urine and feces showed that the 6'-carboxylic acid derivative of etoricoxib was the major metabolite observed (≥65% of the total radioactivity). 6'-Hydroxymethyl-etoricoxib and etoricoxib-1'-N-oxide, as well as the O-β-D-glucuronide conjugate and the 1'-N-oxide derivative of 6'-hydroxymethyl-etoricoxib, were present in the excreta also (individually, ≤10% of the total radioactivity). In healthy male subjects, therefore, etoricoxib is well absorbed, is metabolized extensively via oxidation (6'-methyl oxidation >1'-N-oxidation), and the metabolites are excreted largely in the urine.

Nonsteroidal antiinflammatory drugs are widely used for the treatment of pain, inflammation, and fever. Their mechanism of action involves the inhibition of COX<sup>1</sup>, a hemeoprotein that exists in two forms (COX-1 and COX-2) and converts arachidonic acid to proinflammatory prostaglandins and their subsequent metabolic products (Donnelly and Hawkey, 1997; Jouzeau et al., 1997; Lane, 1997; Lipsky and Isakson, 1997). Because the products of COX-1 are cytoprotective, selective inhibition of COX-2 can reduce inflammation with less of the gastrointestinal side effects characteristic of nonselective nonsteroidal antiinflammatory drugs. Therefore, much attention has been focused on the design of potent and selective COX-2 inhibitors like etoricoxib (5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine; ARCOXIA<sup>2</sup>), which has been developed for acute and chronic analgesia, the treatment of the signs and

symptoms of osteoarthritis, rheumatoid arthritis, dysmenorrhea, and gouty arthritis (Chauret et al., 2001; Ouellet et al., 2001; Riendeau et al., 2001; Sorbera et al., 2001).

Etoricoxib pharmacokinetics are linear at clinically relevant doses and the pharmacokinetic half-life, and pharmacological response, supports oral once-a-day dosing (Agrawal et al., 2001, 2002). In addition, the results of in vitro metabolism studies have indicated that etoricoxib is metabolized via 6'-methyl hydroxylation and 1'-N-oxidation (Fig. 1). These metabolites, which do not inhibit COX-1 and do not contribute significantly to the inhibition of COX-2, are formed by P450s (Chauret et al., 2001; Kassahun et al., 2001). Although the in vitro metabolism of etoricoxib has been described, its absorption, disposition, and metabolism in man have yet to be reported. Therefore, the study presented here describes the absorption and disposition of [<sup>14</sup>C]etoricoxib in human subjects. The specific objectives of this study were 1) to investigate the routes of elimination of etoricoxib in healthy subjects following single oral and i.v. doses of [<sup>14</sup>C]etoricoxib, 2) to quantitate concentrations of total radioactivity and etoricoxib in plasma after single oral and i.v. doses of radiolabeled etoricoxib, 3) to examine the metabolism of etoricoxib in humans, 4) to demonstrate mass balance for [<sup>14</sup>C]etoricoxib in humans, and 5) to estimate the absolute bioavailability of etoricoxib administered as an oral solution.

### Materials and Methods

**Chemicals.** [<sup>14</sup>C]Etoricoxib (>99% radiochemical purity) was synthesized by the Labeled Compound Synthesis Group (Merck Research Laboratories, Rahway, NJ). The Carbon-14 label was incorporated at the methyl group of the methane sulfonyl phenyl moiety (Fig. 1). Standards of the 1'-N'-oxide, 6'-hydroxymethyl, 6'-hydroxymethyl-1'-N'-oxide, and 6'-carboxy metabolites of

<sup>1</sup> Abbreviations used are: COX, cyclooxygenase; etoricoxib (ARCOXIA), 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine; P450, cytochrome P450; HPLC, high performance liquid chromatography; PEG, polyethylene glycol; LC-MS/MS, liquid chromatography tandem mass spectrometry; ESI, electrospray ionization; solvent A, aqueous 0.1% formic acid; solvent B, 0.1% formic acid in acetonitrile; AUC, area under the plasma concentrations versus time curve; Cl, clearance; V<sub>ds</sub>, steady-state volume of distribution; T<sub>max</sub>, time of occurrence of maximal concentration in plasma; AUMC, area under the first moment curve; MRT, mean residence time; τ, infusion time; ANOVA, analysis of variance; GMR, geometric mean ratio; CI, confidence interval.

<sup>2</sup> ARCOXIA is a registered trademark of Merck & Co., Inc.

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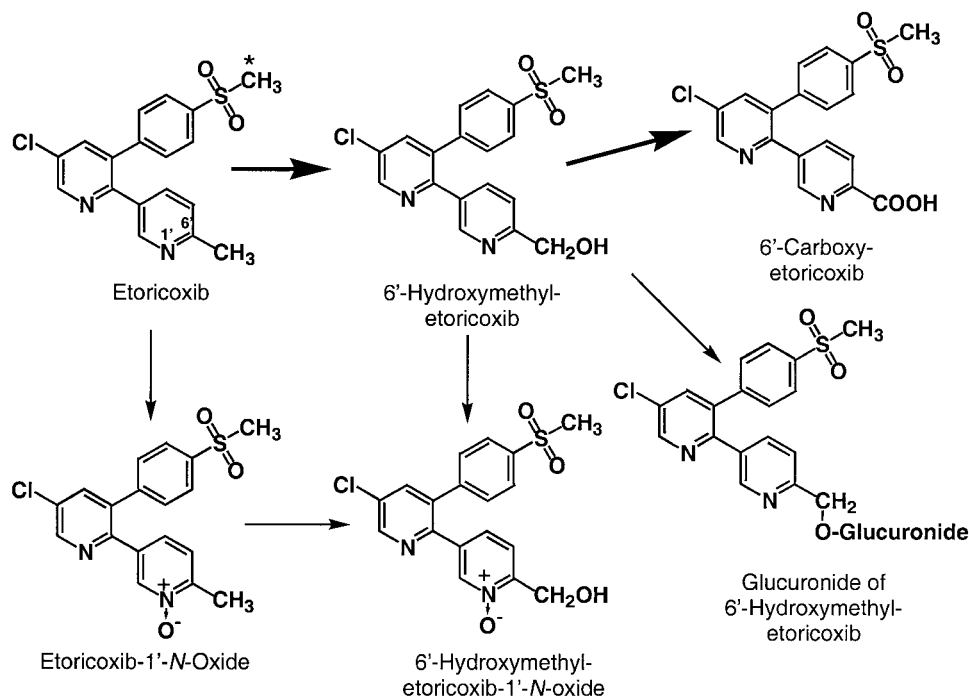


Fig. 1. Proposed metabolic pathways of etoricoxib in healthy human volunteers.

Bolded arrows indicate major pathways. The asterisk denotes the site of the carbon-14 label.

etoricoxib were provided by Drs. Y. LeBlanc and P. Roy (Merck-Frosst Center for Therapeutic Research, Quebec, Canada). Unlabeled etoricoxib was synthesized by the Department of Process Research (Merck Research Laboratories).  $\beta$ -Glucuronidase (*Helix pomatia*, Type H-5) was obtained from Sigma-Aldrich (St. Louis, MO). All other commercially available reagents and solvents were of either analytical or HPLC grade.

**Human Studies.** The study protocol was approved by an Ethics Review Board. All subjects understood the procedures and agreed to participate in the study by giving written informed consent (Declaration of Helsinki).

[ $^{14}\text{C}$ ]Etoricoxib was administered as single doses to six healthy male subjects (open-label, two-period crossover study) as a 15-min intravenous infusion in citrate-buffered saline (100  $\mu\text{Ci}$ , 25 mg; 0.75 mg/ml), or as an oral solution in PEG-400 (100  $\mu\text{Ci}$ , 100 mg; 5.0 mg/ml) via a nasogastric tube to the stomach. The subjects were randomized as to the order of treatments, with a 14-day washout period between treatments. Heparinized blood was collected at intervals through 168 h (7 days). The plasma was separated and stored at  $-20^\circ\text{C}$ . Urine and feces were collected for 7- and 10-day periods, respectively, and stored at  $-20^\circ\text{C}$ .

**Measurement of Total Radioactivity.** Plasma and urine samples were thawed at room temperature and mixed thoroughly. After centrifugation of plasma to remove the fibrin, aliquots (0.5 or 1.0 ml) were transferred to polyethylene vials, and 15 ml of scintillation cocktail (Ready-Safe; Beckman Coulter, Inc., Fullerton, CA) was added for counting in a Beckman LS 5000CE liquid scintillation spectrometer (Beckman Coulter Inc.). Urine samples were thawed overnight at  $4^\circ\text{C}$ , and 1-ml aliquots were transferred to vials for counting as described for plasma.

Fecal samples were thawed overnight at  $4^\circ\text{C}$ . Samples were transferred to a tared 1-liter beaker. The original containers were thoroughly rinsed with water, which was added to samples. Additional water was added, and the samples were homogenized to a slurry (OMNI Mixer Homogenizer; Omni International Inc., Warrenton, VA). Total homogenate weights were recorded. Aliquots of the homogenates ( $2 \times \sim 1\text{g}$ ) were transferred to tared combustion cups weighed, and allowed to dry overnight in a hood. The samples were subjected to combustion in a tissue oxidizer (model 306B, Packard) and counted for radioactivity as above.

**Preparation of Plasma Samples for Etoricoxib Assay.** Concentrations of etoricoxib in plasma samples were determined using previously described methodology (Matthews et al., 2001). In brief, the method involves solid-phase

extraction in the 96-well format of etoricoxib from plasma followed by HPLC with postcolumn photochemical cyclization and fluorescence detection of the plasma extracts. The method is linear over the concentration range of 5 to 500 ng/ml etoricoxib. Based on the replicate analyses of spiked standards, the within-day precision was better than 7% at all points on the calibration curve, whereas within-day accuracy was within 5% of nominal at all standard concentrations. The lower limit of quantitation was 5.0 ng/ml.

**Preparation of Plasma, Urine, and Fecal Samples for Metabolite Profile Analysis.** *Plasma.* Samples collected at 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12, 15, 18, 21, and 24 h after intravenous (25 mg) administration, and at 0.5, 1, 2, 4, 6, 8, 10, 12, 15, 18, 21, and 24 h after oral (100 mg) dosing, were thawed at room temperature. For each subject, aliquots (0.5 ml, i.v.; 1.0 ml, p.o.) from each sample were pooled for a total volume of 7 ml (i.v.) and 12 ml (p.o.) plasma. An aliquot (0.5 ml) was taken from each pooled sample for liquid scintillation counting. The plasma proteins in the remaining samples were precipitated by the addition of four volumes of 1.5% glacial acetic acid in acetonitrile/methanol (2:1) while vortexing vigorously. After centrifugation, the supernatants were transferred to clean tubes, and an aliquot (1 ml) was taken for liquid scintillation counting. Recovery of radioactivity after extraction was  $\geq 90\%$ . The supernatants were evaporated to dryness in the SpeedVac concentrator. The residues were reconstituted in 400  $\mu\text{l}$  of 25 mM ammonium acetate (pH 7), and the solutions were transferred to autosampler vials for radiochromatography. The injection volume was 300  $\mu\text{l}$ . The remaining material was submitted for evaluation by mass spectrometry.

*Urine.* Samples from 0- to 2-, 2- to 4-, 4- to 6-, 6- to 9-, 9- to 12-, 12- to 18-, and 18- to 24-h collection intervals after i.v. and oral administration (all subjects) were thawed at room temperature and mixed vigorously. Aliquots from each time interval were combined in proportion to their respective volumes to produce a representative 0- to 24-h sample for each subject. A 200- $\mu\text{l}$  aliquot of the pooled mixture was taken for scintillation counting. To concentrate the urine samples prior to radiochromatography, aliquots (5 ml) were transferred to glass centrifuge tubes, and trifluoroacetic acid (15  $\mu\text{l}$ ) was added to acidify the samples to approximately pH 3. Acetonitrile (20 ml) was added with mixing, and particulate material was removed by centrifugation ( $\sim 3000$  rpm, 10 min). The supernatants were transferred to 50-ml glass tubes, and the solvent was removed in a centrifugal vacuum concentrator (SpeedVac, Savant Instruments, Holbrook, NY). The residues were reconstituted in 300  $\mu\text{l}$  of 20% acetonitrile in 25 mM ammonium acetate, pH 7 (v/v), and the solutions

were sonicated and transferred to autosampler vials for radiochromatography (injection volume of 200  $\mu$ l). The remaining material of selected samples was submitted for evaluation by mass spectrometry. Urine samples from 24- to 36- and 36- to 48-h intervals were combined in proportion to their respective volumes to provide a representative 24- to 48-h sample. The samples (5 ml each) were extracted and prepared for chromatography as above. Selected samples were submitted for evaluation by mass spectrometry.

**Feces.** Homogenized fecal samples (selected subjects) were thawed at room temperature and mixed thoroughly. Duplicate 1-ml aliquots were transferred to glass tubes and 4 ml of 1.5% glacial acetic acid in acetonitrile/methanol (2:1) was added while mixing. The samples were homogenized with a hand-held tissue homogenizer (Tissue Tearor, Biospec Products Inc., Bartlesville, OK) and sonicated for 2 min, and this homogenization-sonication step was then repeated. After centrifugation, the supernatants were transferred to clean tubes, and aliquots (100  $\mu$ l) were taken for liquid scintillation counting. Recovery of radioactivity was good (>95%). The supernatants were evaporated to dryness in the SpeedVac concentrator, and the residues were reconstituted in 250  $\mu$ l of 25 mM ammonium acetate (pH 7) followed by the addition of 50  $\mu$ l of acetonitrile. The samples were transferred to autosampler vials for radiochromatography (200  $\mu$ l injected), and the remaining reconstituted material was submitted for evaluation by mass spectrometry.

**Conditions for Radiochromatography of Plasma, Urine, and Fecal Extracts.** The above samples were subjected to chromatography on a HP1100 chromatograph system (Hewlett Packard, Palo Alto, CA). The metabolites were separated on a Zorbax Eclipse XDS C<sub>8</sub> column (4.6  $\times$  250 mm) eluted at a flow rate of 1 ml/min using a linear gradient starting at 20% acetonitrile in 25 mM ammonium acetate (pH 7) and increasing to 50% acetonitrile at 1%/min for a total run time of 30 min. The column was maintained at 40°C in an oven compartment. A post-run time of 5 min under starting mobile phase conditions permitted re-equilibration of the column. The effluent was monitored by UV at 280 and 236 nm (photodiode array detector) and by an in-line radiochemical detector ( $\beta$ -RAM model 2B, IN/US, Tampa, FL), using a 3 ml/min flow rate for the scintillation cocktail (flow rate of 4 ml/min through the radiochemical detector).

**Fractionation of Pooled Urine for Metabolite Identification by LC-MS/MS.** Aliquots (~20 ml) of pooled 0- to 24-h urine were acidified to pH 3 with trifluoroacetic acid, and 5  $\times$  1.1 ml was transferred to autosampler vials for injection (2  $\times$  500  $\mu$ l per vial) onto the HPLC column using the conditions described above. The effluent was collected with the aid of a fraction collector (ISCO Foxy-200; Isco Inc., Lincoln, NE) as 1-min fractions (1 ml/min). A total of 10 injections were made. An aliquot (0.5 ml) from each fraction (10 ml of total volume) was taken for liquid scintillation counting, and a histogram was constructed. Those fractions containing  $\geq$ 2% of the total radioactivity were evaporated to dryness using a rotary evaporator. The residues were dissolved in acetonitrile, or a 2:1 mixture of acetonitrile and water, and the solutions were transferred to autosampler vials. Solvent was evaporated to dryness (N<sub>2</sub>, 44°C), and the residues were submitted for mass spectrometry.

**Conditions for LC-MS/MS.** Chromatography was conducted on a HP1090 chromatograph (Hewlett Packard) interfaced to a Finnigan TSQ tandem mass spectrometer (Thermo Finnigan, San Jose, CA). Separation of metabolites was carried out on a Phenomenex Luna C<sub>18</sub> (2) column (2.0  $\times$  250 mm, 5  $\mu$ m; Phenomenex, Torrance, CA) using a mobile phase consisting of 0.1% formic acid in Milli-Q water (solvent A) and 0.1% formic acid in acetonitrile (solvent B) at a constant flow rate of 0.2 ml/min. The gradient conditions were as follows: isocratic conditions starting at 10% B were maintained for 3 min followed by a linear increase to 25% B over 2 min. The concentration of B was slowly increased to 35% over the next 20 min, followed by a rapid increase to 80% B over 2 min. The column was washed at 80% B for 5 min, and conditions were returned to 10% B over 3 min. The system was equilibrated for 10 min at 10% B prior to each injection. Total run time was 27 min prior to washing and equilibration of the column.

Mass spectral analyses were carried out using ESI in the positive ion mode. The ESI-ionizing voltage was maintained at 5.0 kV for all analyses. MS/MS was based on collision-induced dissociation of ions entering the rf-only octapole region, where argon was used as the collision gas at a pressure of 1.7 torr. A combination of collision offsets ranging from -25 eV to -45 eV was used for all MS/MS analyses.

**Chromatographic Conditions to Separate Two Coeluting Metabolites.**

The 6'-carboxylic acid metabolite and the *O*- $\beta$ -D-glucuronide of 6'-hydroxymethyl-etoricoxib were found to coelute using the neutral pH chromatographic conditions described above. Changing the elution conditions to an acidic mobile phase permitted separation of the two components. Under these conditions, the amount of the 6'-hydroxymethyl-etoricoxib glucuronide could be estimated.

Urine and fecal samples were prepared for chromatography as described above and injected onto a Phenomenex Luna C<sub>18</sub>(2) column (4.6  $\times$  250 mm). The mobile phase consisted of aqueous 0.1% formic acid (solvent A) and 0.1% formic acid in acetonitrile (solvent B). The metabolites were eluted at a flow rate of 1 ml/min using a linear gradient starting at 10% solvent B and increasing to 50% solvent B at 1%/min (total run time of 40 min). All other conditions were as described above. The metabolites separated with baseline resolution and with good peak shape under these conditions, except for the 6'-carboxylic acid metabolite, which eluted as a very broad, tailing peak that did not permit reproducible integration.

**Incubation of Urine and Fecal Homogenates with  $\beta$ -Glucuronidase.** Two-milliliter aliquots of urine (0–24 h) and 0.9 ml of fecal homogenates were transferred to glass tubes. One milliliter of  $\beta$ -glucuronidase solution (2 mg/ml in 0.2 M sodium acetate, pH 5.2) was added to each tube. A second set of samples was prepared to which 1 ml of the sodium acetate buffer was added to serve as control. All the samples were incubated overnight at 37°C in a shaking water bath. The reaction was stopped with the addition of 4 volumes of 1.5% acetic acid in acetonitrile/methanol (2:1). After centrifugation, the supernatants were transferred to clean tubes, and the solvent was evaporated to dryness in the SpeedVac concentrator. The residues were reconstituted in 300  $\mu$ l (urine) and 500  $\mu$ l (feces) of 20% acetonitrile in 25 mM ammonium acetate, pH 7 (v/v), and the solutions were sonicated and transferred to autosampler vials for radiochromatography under neutral pH conditions. Injection volumes were 200  $\mu$ l (urine) and 400  $\mu$ l (feces).

**Identification and Quantitation of Metabolites.** Authentic standards of etoricoxib ([M + H]<sup>+</sup> ion at *m/z* 359) and its phase I metabolites (the 6'-hydroxymethyl, 6'-carboxylic acid, 1'-*N*-oxide, and 6'-hydroxymethyl-1'-*N*-oxide derivatives) were available to support the characterization of etoricoxib metabolites by similarity of chromatographic retention time and their respective UV spectra. Further support of their identification was provided by mass spectroscopy (6'-hydroxymethyl, [M + H]<sup>+</sup> ion at *m/z* 375; 6'-carboxylic acid, [M + H]<sup>+</sup> ion at *m/z* 389; 1'-*N*-oxide, [M + H]<sup>+</sup> ion at *m/z* 375; and 6'-hydroxymethyl-1'-*N*-oxide, [M + H]<sup>+</sup> ion at *m/z* 391). The structure of the glucuronide conjugate of 6'-hydroxymethyl-etoricoxib was verified by mass spectroscopy. The [M + H]<sup>+</sup> ion at *m/z* 551 was consistent with a glucuronic acid conjugate of a mono-oxygenated metabolite of etoricoxib. The product ion spectrum generated upon collision-induced dissociation of the [M + H]<sup>+</sup> ion was consistent with a structural assignment of an *O*- $\beta$ -D-glucuronide of the 6'-hydroxymethyl metabolite.

The metabolites were quantitated based on the percentage of total radioactivity for each peak observed under neutral pH chromatographic conditions. The major radioactive peak, however, contained two coeluting components, namely, the 6'-carboxylic acid derivative and the *O*- $\beta$ -D-glucuronide conjugate of 6'-hydroxymethyl-etoricoxib. Under acidic chromatographic conditions, the two components could be separated, but the peak shape of the carboxylic acid was very poor. Consequently, the percentage of total radioactivity obtained for the glucuronide conjugate under acidic conditions was subtracted from the value for the pair of coeluting metabolites observed under neutral conditions to provide the percentage of radioactivity attributed to the 6'-carboxylic acid.

**Pharmacokinetic Methods.** Plasma concentrations of etoricoxib and radioactivity, and actual sampling times relative to the etoricoxib dose, were used to estimate pharmacokinetic parameters for each treatment in each subject (AUC<sub>∞</sub>, *t*<sub>1/2</sub>, Cl, and *V*<sub>dss</sub> for the i.v. dose; and AUC<sub>∞</sub>, C<sub>max</sub>, *T*<sub>max</sub>, and apparent *t*<sub>1/2</sub> for the oral dose). The C<sub>max</sub> and *T*<sub>max</sub> were obtained by inspection of the concentration-time data. The terminal *t*<sub>1/2</sub> 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 (Yeh and Remphrey, 1990). The area under the plasma concentration-time curve (AUC<sub>∞</sub>) and the area under the first moment curve (AUMC) (following i.v. administration) were calculated using the linear trapezoidal method up to the last measured concentration. The additional area was estimated from the last measured

concentration, and the value of  $t_{1/2}$  (<3% of the total AUC was extrapolated). Plasma clearance was calculated from i.v. data as the ratio of dose to AUC. For each individual, the actual i.v. dose administered was used (the weight of the dosing solution administered divided by the formulation density multiplied by the assayed potency of the dosing solution administered; i.v. potency = 0.746 mg/ml; and formulation density = 1.005 g/ml). The steady-state volume of distribution ( $V_{dss}$ ) was calculated as

$$V_{dss} = Cl \cdot MRT = \frac{Dose_{i.v.} \left[ \frac{AUMC}{AUC} - \frac{\tau}{2} \right]}{AUC}$$

where MRT is the mean residence time and  $\tau$  is the infusion time.

Absolute bioavailability was assessed by dose-adjusted AUC ratios (oral/i.v.), where the actual i.v. and oral doses administered were used, calculated as described above (oral solution potency = 4.94 mg/ml; and formulation density = 1.128 g/ml).

**Statistical Methods.** Pharmacokinetic parameters ( $AUC_{\infty}$  for the i.v. and oral solutions and  $C_{max}$  for the oral solution) for etoricoxib and total radioactivity following a single dose were analyzed using an analysis of variance (ANOVA) model containing factors for subject and treatment (equivalent to a paired  $t$  test). The natural log transformation was applied to  $AUC_{\infty}$  and  $C_{max}$  data. Prior to statistical analyses, the  $AUC_{\infty}$  and  $C_{max}$  data were adjusted for the actual dose administered.

To estimate the proportion of total radioactivity accounted for by etoricoxib in plasma, the  $AUC_{\infty}$  and  $C_{max}$  GMRs of etoricoxib-to-radioactivity for both the i.v. and oral solutions were computed along with corresponding 95% confidence intervals (CIs). Each CI was first computed on the difference between the treatments on the natural log scale using the  $t$ -distribution and mean square error from the above ANOVA model. The upper and lower limits were then exponentiated to obtain the CI for the GMR for  $AUC_{\infty}$  and  $C_{max}$ .

To estimate bioavailability of the oral solution, appropriate pharmacokinetic parameters following the single-dose administrations of oral and i.v. solutions were compared using an ANOVA model appropriate for a 2-period, crossover study containing factors for sequence, subject-within-sequence, period, and treatment. The sequence effect was tested against the subject-within-sequence term and was found to be nonsignificant. An estimate of oral bioavailability was based upon the  $AUC_{\infty}$  GMR between the 100-mg oral dose and the 25-mg i.v. dose. A 95% CI of the dose-adjusted oral/i.v. ratio was constructed using the methodology as described above for obtaining the corresponding interval for this GMR. Summary statistics for clearance,  $V_{dss}$ , and  $t_{1/2}$  following the i.v. dose as well as summary statistics for  $T_{max}$  and apparent  $t_{1/2}$  following the oral solution were also determined. The normality assumption of the above ANOVA models was tested using the Shapiro-Wilk statistic, and the homogeneity of variance assumption of the ANOVA model was tested using graphical techniques. The use of the transformed data generally satisfied the assumptions of the ANOVA model, thus, confirming the appropriateness of the transformations. All pharmacokinetic parameters were back-transformed to the original scale for presentation purposes.

## Results

**Absorption and Excretion of [ $^{14}C$ ]Etoricoxib.** The mean concentration-time profiles of etoricoxib and radioactivity in plasma following i.v. and oral administration are shown in Fig. 2, and the geometric mean AUC ratios of etoricoxib-to-total radioactivity (95% CI) were 0.73 (0.70, 0.76) and 0.75 (0.70, 0.82), respectively, indicating that etoricoxib accounts for the majority of the radioactivity in plasma following either route of administration. Following the i.v. dose, clearance was low (57 ml/min), and the harmonic mean  $t_{1/2}$  was 24.8 h (Table 1). The absolute bioavailability of the oral solution was estimated to average 83%, with a  $T_{max}$  and  $C_{max}$  of 1 h and 1.36  $\mu$ g/ml, respectively.

The mean total recovery of radioactivity was 90.4% (i.v.) and 80.3% (p.o.) in the excreta (Table 2). Excretion was primarily by the renal route with 70.1% (i.v.) and 60.0% (p.o.) of the dose eliminated in urine. Radioactivity in the feces accounted for ~20% of the dose following either route of administration. Because the recovery of

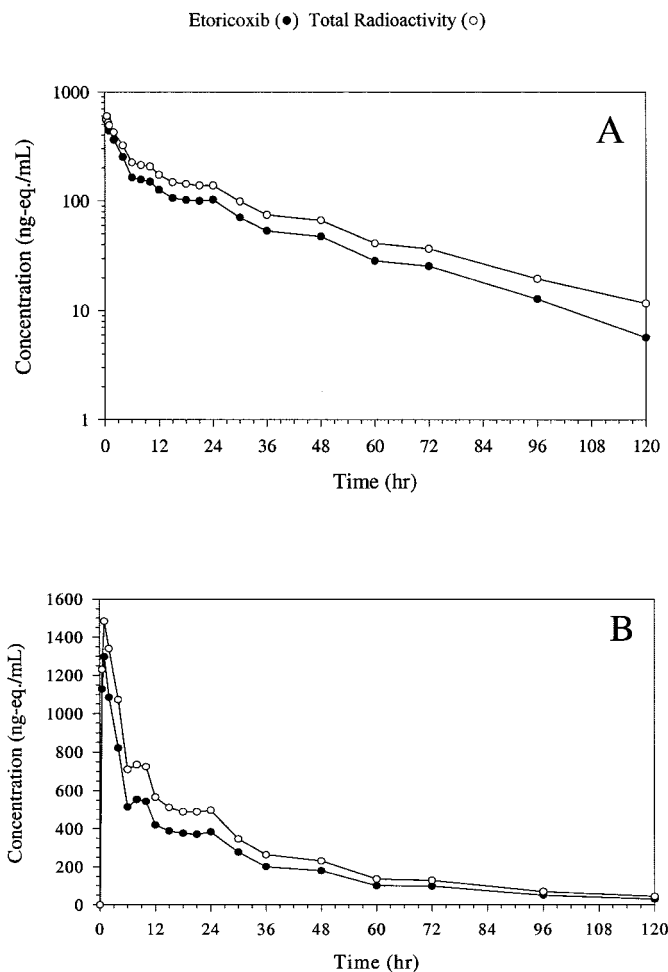


Fig. 2. Mean concentrations of etoricoxib (nanograms per milliliter) and total radioactivity (nanograms  $\cdot$  equivalents per milliliter) in plasma following administration of a single dose of [ $^{14}C$ ]etoricoxib to six healthy male volunteers: (A) i.v. dose (25 mg, 100  $\mu$ Ci), and (B) p.o. dose (100 mg, 100  $\mu$ Ci).

radioactivity in the urine was independent of dose route, it was concluded that etoricoxib is well absorbed (~86% as total drug equivalents).

**Metabolism of [ $^{14}C$ ]Etoricoxib.** Radiochromatograms of 0- to 24-h pooled urine from the six subjects were qualitatively and quantitatively similar following i.v. and p.o. administration of [ $^{14}C$ ]etoricoxib (Fig. 3). Mass spectral analysis of concentrated urine samples, and of isolated metabolite fractions, demonstrated that the 6'-carboxylic acid metabolite and the  $O$ - $\beta$ -D-glucuronide conjugate of 6'-hydroxymethyl-etoricoxib both contributed to the radioactivity of the major peak (retention time = 9 min). By changing from a Zorbax  $C_8$  base-deactivated column to a Phenomenex Luna  $C_{18}(2)$  column, and eluting with an acidic mobile phase, the two components were separated (Fig. 3), permitting quantitation of the glucuronide conjugate in the samples.

Radiochromatograms of pooled urine (0-24 h), feces, and plasma from a human subject after i.v. administration are shown in Fig. 4. The major peak (retention time = 9 min) represents the coeluting 6'-carboxylic acid derivative of etoricoxib and the 6'-hydroxymethyl-etoricoxib glucuronide conjugate. After correction for the amount of glucuronide conjugate present, the 6'-carboxylic acid was the major metabolite observed, comprising 78-80% of the total radioactivity in 0- to 24-h urine, or 26 to 27% of the dose (Table 3). The  $O$ - $\beta$ -D-glucuronide conjugate of 6'-hydroxymethyl-

TABLE 1

Mean pharmacokinetic parameters of etoricoxib following administration of a single 25-mg intravenous and 100-mg oral solution dose of [ $^{14}\text{C}$ ]etoricoxib to six healthy male volunteers

Route of Administration	Dose	AUC $_{\infty}$ <sup>a</sup>	C $_{\text{max}}$ <sup>a</sup>	T $_{\text{max}}$ <sup>b</sup>	t $_{1/2}$ <sup>c</sup>	Clearance <sup>a</sup>	V $_{\text{dss}}$ <sup>d</sup>	Bioavailability <sup>e</sup>
	mg	$\mu\text{g} \cdot \text{h/ml}$	ng/ml	h	h	ml/min	liter	%
i.v.	25	7.4 (2.1)			24.8 (6.9)	57 (16)	108 (26)	
p.o.	100	24.4 (8.8)	1362 (333)	1.0 (0.5, 2.0)	24.9 (6.0)			83 (71, 97)

<sup>a</sup> Geometric mean (between-subject S.D.).

<sup>b</sup> Median (min, max).

<sup>c</sup> Harmonic mean (jackknife S.D.).

<sup>d</sup> Arithmetic mean (S.D.).

<sup>e</sup> Geometric mean (95% CI).

TABLE 2

Mean recovery of radioactivity in urine and feces following i.v. (25 mg) and p.o. (100 mg.) administration of [ $^{14}\text{C}$ ]etoricoxib (100  $\mu\text{Ci}$ ) to six healthy male subjects

Sample	Interval	Percent of Dose Recovered <sup>a</sup>			
		Oral		i.v.	
		Mean	S.D.	Mean	S.D.
Urine	<i>h</i>				
	0-2	2.96	0.98	2.40	1.03
	2-4	6.33	1.48	5.11	3.47
	4-6	3.62	1.51	5.71	2.92
	6-9	5.53	2.09	4.78	1.64
	9-12	5.39	1.99	7.91	2.44
	12-18	3.85	2.27	4.59	3.22
	18-24	5.62	4.54	4.35	1.86
	24-36	7.83	1.23	11.20	4.66
	36-48	5.14	1.35	7.23	3.31
	48-72	5.83	1.42	8.19	3.13
	72-96	4.16	1.24	3.58	1.87
	96-120	2.17	1.66	2.70	1.57
	120-168	1.58	2.04	2.34	2.47
Sub Total	60.0	5.50	70.1	12.1	
Feces	0-24	2.17	2.04	1.00	1.63
	24-48	3.92	2.64	5.40	4.42
	48-72	7.48	4.62	6.84	3.81
	72-96	2.55	2.18	3.31	2.62
	96-120	1.82	1.55	1.53	1.59
	120-144	0.79	0.75	1.83	2.27
	144-168	0.71	0.83	0.73	0.53
	168-192	0.56	0.93	0.33	0.34
	192-216	0.13	0.23	0.07	0.06
	216-240	0.15	0.21	0.25	0.53
	Sub Total	20.3	7.84	20.4	6.59
Urine and Feces	Total	80.3	7.10	90.4	13.3

<sup>a</sup> Data represent mean and S.D. ( $n = 6$  subjects).

etoricoxib comprised 6 to 7% of the total radioactivity (~2% of the dose) in these samples. These results were supported by the incubation of urine with  $\beta$ -glucuronidase in which a decrease in the major peak and a concomitant increase in the 6'-hydroxymethyl peak was observed (data not shown). 6'-Hydroxymethyl-etoricoxib and etoricoxib-1'-N-oxide, as well as the 1'-N-oxide derivative of 6'-hydroxymethyl-etoricoxib, each constituted 1.7 to 4.2% of the total radioactivity (0.6-1.5% of the dose) in urine. Only ~1% of the total radioactivity (0.3% of the dose) was present as unchanged drug in 0- to 24-h urine (Table 3). Although a standard of the 6'-carboxylic acid acyl glucuronide was not available, every effort was made to process and analyze the samples under acidic conditions (pH ~3), and there was no LC-MS/MS or radiochromatographic evidence for its formation. Radiochromatographic profiles of the 24- to 48-h urine were qualitatively and quantitatively similar to those obtained for the 0- to 24-h samples (data not shown). Given the similarity of the profiles for the 0- to 24-h and

24- to 48-h urine samples, representing 34.9 and 18.4% (i.v.) and 33.3 and 13.0% (p.o.) of the dose, respectively, the characterization of the 0- to 24-h urine described the overall metabolism of etoricoxib (Fig. 1).

The 6'-carboxylic acid derivative was the major metabolite (~70% of the total radioactivity) observed in radiochromatograms of selected fecal extracts, although the 6'-hydroxymethyl-1'-N-oxide (~10%) and 6'-hydroxymethyl (~5%) were detected also (Fig. 4). When extracts were subjected to chromatography under acidic conditions, there was no evidence for the presence of the glucuronide conjugate of 6'-hydroxymethyl-etoricoxib, an observation that was supported by incubation of fecal homogenates with  $\beta$ -glucuronidase (data not shown). It is highly likely that the glucuronide, once secreted into bile, was hydrolyzed by gut bacteria. In addition, the low level of parent drug in feces, following the i.v. and p.o. dose, was indicative of good absorption and minimal biliary secretion.

Plasma extracts, pooled over the interval from the first time

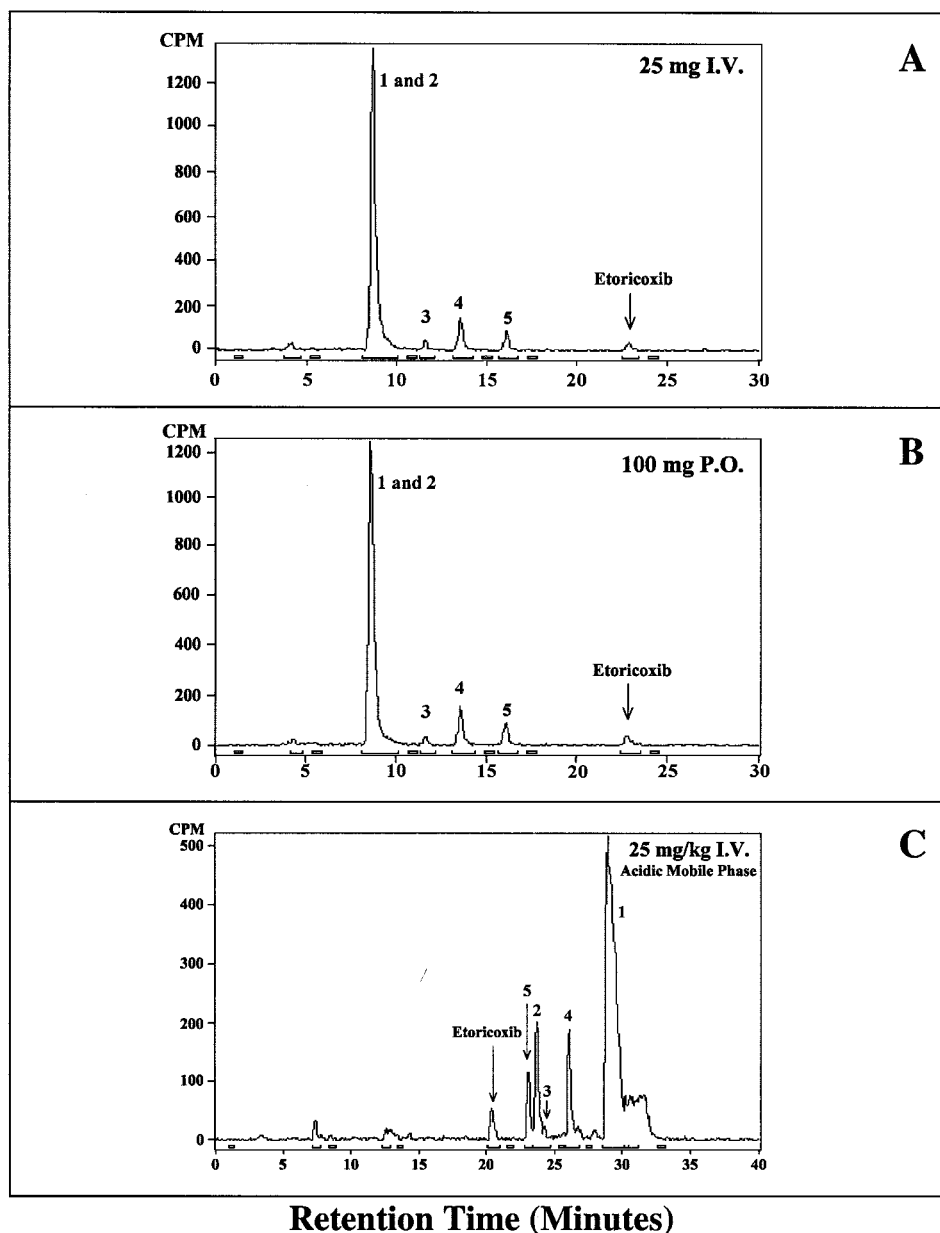


FIG. 3. Representative radiochromatograms of extracts from urine (0–24 h) of a human subject following i.v. (A) and oral (B) administration of [ $^{14}\text{C}$ ]etoricoxib obtained under neutral pH mobile phase conditions and an extract run under acidic mobile phase conditions (C).

Metabolite peaks are identified as **1**, 6'-carboxy-etoricoxib; **2**, 6'-hydroxymethyl-etoricoxib *O*- $\beta$ -D-glucuronide; **3**, 6'-hydroxymethyl-etoricoxib-1'-*N*-oxide; **4**, etoricoxib-1'-*N*-oxide; and **5**, 6'-hydroxymethyl-etoricoxib.

point through 24 h, were subjected to radio-LC and LC-MS/MS analysis also. In agreement with the data presented in Fig. 2, etoricoxib was the major component and comprised 83% (i.v.) and 71% (p.o.) of the total radioactivity present therein (Fig. 4). The 6'-hydroxymethyl metabolite constituted 7 to 10% of the total radioactivity after i.v. and oral dosing, but the 6'-carboxylic acid (4%) was observed only in the plasma following p.o. administration (data not shown).

Therefore, etoricoxib was extensively metabolized in human subjects who received a single i.v. (25 mg) and p.o. (100 mg) dose of [ $^{14}\text{C}$ ]etoricoxib. The 6'-carboxylic acid derivative was the major metabolite excreted in urine and feces after either dose. 6'-Hydroxymethyl-etoricoxib, etoricoxib-1'-*N*-oxide, the 1'-*N*-oxide of 6'-hydroxymethyl-etoricoxib, and the *O*- $\beta$ -D-glucuronide conjugate of the 6'-hydroxymethyl derivative each comprised  $\leq 7\%$  of the total

radioactivity in 0- to 24-h urine. In feces, 6'-hydroxymethyl-etoricoxib and the 1'-*N*-oxide of 6'-hydroxymethyl-etoricoxib each constituted  $\leq 11\%$  of the total radioactivity.

### Discussion

The purpose of this study was to investigate the absorption, disposition, and mass balance of [ $^{14}\text{C}$ ]etoricoxib in healthy male volunteers. Mass balance was reasonably achieved, with total recovery of radioactivity averaging 80 and 90% of dose following oral and i.v. administration of [ $^{14}\text{C}$ ]etoricoxib, respectively. Recovery of radioactivity averaged 60% of dose in urine following oral administration, 70% of dose in urine following i.v. administration, and 20% in feces following either route of administration. In addition, the plasma concentration profiles following administration of both i.v. and oral doses indicate that etoricoxib accounted for the majority of the radio-

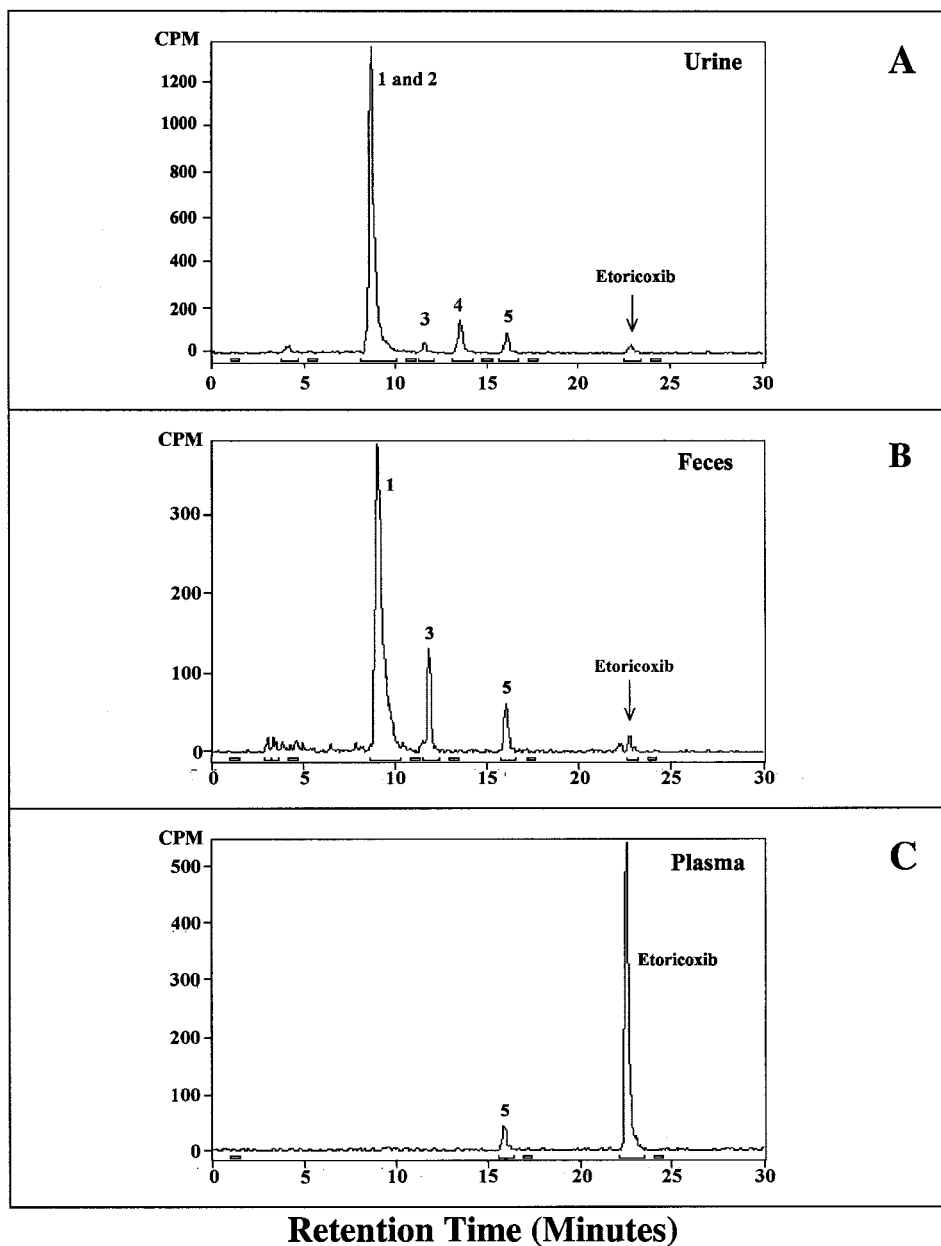


FIG. 4. Representative radiochromatograms of extracts of 0 to 24 h urine (A), day 2 feces (B), and pooled (0.25 to 24 h) plasma (C) of a human subject following i.v. administration of [ $^{14}\text{C}$ ]etoricoxib (25 mg, 100  $\mu\text{Ci}$ ) obtained under neutral mobile phase conditions.

Metabolite peaks are identified as **1**, 6'-carboxy-etoricoxib; **2**, 6'-hydroxymethyl-etoricoxib *O*- $\beta$ -D-glucuronide; **3**, 6'-hydroxymethyl-etoricoxib-1'-*N*-oxide; **4**, etoricoxib-1'-*N*-oxide; and **5**, 6'-hydroxymethyl-etoricoxib.

activity in plasma ( $\sim 75\%$ ). The concentrations of etoricoxib and radioactivity declined in parallel, suggesting either reversible metabolism or formation rate-limited metabolic elimination. Since the metabolism of etoricoxib did not appear to be reversible, the parallel decline is likely a result of formation rate-limited metabolic elimination.

The results also showed that radiolabeled etoricoxib was well absorbed following administration of an oral solution in PEG, and the absolute bioavailability averaged 83% (range of 70–99%). This oral bioavailability is somewhat lower than that reported for tablet formulations ( $\sim 100\%$ ), although the  $T_{\text{max}}$  and apparent  $t_{1/2}$  of the two formulations were similar (Agrawal et al., 2001, 2002). However, this result is consistent with that from a previous study, in which the tablet formulation of etoricoxib was found to be slightly more bioavailable

than an oral solution in PEG (N. G. B. Agrawal, unpublished). It is assumed that the hepatic extraction is low, because the observed mean plasma clearance following the i.v. dose was low (57 ml/min, blood-to-plasma ratio approaches unity; Kassahun et al., 2001) relative to hepatic blood flow ( $\sim 1500$  ml/min; Davies and Morris, 1993). Assuming that the i.v. dose is only metabolized by the liver, the hepatic extraction is calculated to be  $\sim 0.04$ . With negligible gut first pass metabolism, the oral bioavailability (fraction bioavailable  $\sim 0.83$ ) can be readily calculated based on the product of the fraction absorbed (0.86) and the estimated fraction surviving hepatic first pass (0.96).

Analysis of the excreta for etoricoxib and metabolites demonstrated that etoricoxib is metabolized extensively. Less than 1% of an administered i.v. and oral dose was recovered intact in urine over the first 24 h postdose, indicating that renal excretion plays a minimal role in

TABLE 3

Quantitation of etoricoxib metabolites as the percent of total radioactivity in human urine (0–24 hr) following i.v. (25 mg) and p.o. (100 mg) administration of [<sup>14</sup>C]etoricoxib

Subject Number	Dose Route	Percent of Total Radioactivity Excreted in Urine (0–24 hr) as Etoricoxib and Its Metabolites <sup>a,b</sup>					
		6'-Carboxy-etoricoxib	6'-Hydroxy-methyl-etoricoxib Glucuronide	6'-Hydroxy-methyl-etoricoxib-1'-N-oxide	Etoricoxib-1'-N-oxide	6'-Hydroxy-methyl-etoricoxib	Etoricoxib
Mean	i.v.	78.1	6.78	1.91	4.20	2.65	0.81
S.D.		3.85 (27.2)	1.38 (2.40)	0.64 (0.70)	1.78 (1.50)	1.00 (0.90)	0.58 (0.30)
Mean	p.o.	79.7	5.99	1.70	4.04	2.48	0.90
S.D.		5.29 (26.5)	1.78 (2.00)	0.66 (0.60)	2.39 (1.30)	1.29 (0.80)	0.81 (0.30)

<sup>a</sup> Data represent mean and S.D. of  $n = 6$  subjects. The data in parentheses represent the mean percent of the dose recovered in urine as unchanged etoricoxib and each of its metabolites (percent of dose in 0–24 h urine was 34.9 and 33.3% after the i.v. and p.o. dose, respectively).

<sup>b</sup> The total amount of radioactivity accounted for as parent and metabolites in 0–24 h urine after i.v. and p.o. dosing is 95%.

the elimination of etoricoxib. However, the metabolites of etoricoxib are largely excreted renally, because the recovery of radioactivity in urine averaged >60% of dose. In fact, the 6'-carboxylic acid metabolite accounted for the majority of the radioactivity in urine (~80%), over the first 24 h postdose, and small amounts of four other metabolites were found also, including the etoricoxib 1'-N-oxide (~4%), 6'-hydroxymethyl-etoricoxib (~3%), the 1'-N-oxide of 6'-hydroxymethyl-etoricoxib (~2%), and the glucuronide of 6'-hydroxymethyl-etoricoxib (~7%) (Fig. 1). Similarly, the majority of the radioactivity in feces was accounted for by the 6'-carboxylic acid metabolite (65 and 70% following i.v. and oral administration, respectively), and less than 2% was recovered as etoricoxib. Since the recovery of radioactivity in urine and feces was similar following i.v. and oral administration, the presence of radioactivity in feces (20% of dose) is likely attributable to biliary secretion of etoricoxib (minor) and its metabolites.

The observation that hydroxylation of the 6'-methyl moiety predominated over 1'-N-oxidation is in accord with the results of prospective in vitro studies (Chauret et al., 2001; Kassahun et al., 2001), and preclinical metabolism and disposition studies with rats and dogs (R. A. Halpin, unpublished). The in vitro data show that the oxidative metabolism is catalyzed by multiple P450s in the presence of NADPH-fortified human liver microsomes, with CYP3A4 playing an important role (~60%), and the remainder of the activity shared more or less equally among other P450s (e.g., CYP2C9, 2D6, 1A2, and 2C19) (Kassahun et al., 2001). In addition, the oxidation of the 6'-hydroxymethyl to the corresponding 6'-carboxylic acid requires human liver cytosol and NAD<sup>+</sup> (D. E. Slaughter, unpublished). All of these metabolites have been tested for COX-1 and COX-2 inhibitory activity in vitro. None are active as inhibitors in the COX-1 whole blood assay, and only the 1'-N-oxide and the 6'-carboxylic acid show weak activity in the COX-2 assay (IC<sub>50</sub> values of approximately 20 μM versus approximately 1 μM for etoricoxib) (Chauret et al., 2001). Because of the low levels in plasma and weak COX-2 activity, the metabolites of etoricoxib are unlikely to contribute to the inhibition of COX-2 in vivo.

In some respects, the profile of etoricoxib is similar to that of other COX-2-selective agents such as rofecoxib, valdecoxib, and celecoxib, which are well absorbed and metabolized extensively. However, rofecoxib undergoes reductive as well as oxidative metabolism (Halpin et al., 2002), whereas valdecoxib is metabolized by P450s (CYP3A4 and CYP2C9) and undergoes direct glucuronidation (Karim et al., 2001; Yuan et al., 2002). Like etoricoxib, celecoxib is metabolized extensively via methyl hydroxylation, with further oxidation to the corresponding carboxylic acid (Paulson et al., 2000). However, the primary oxidative step is catalyzed largely by a single P450

(CYP2C9), and the drug interaction profile is different from that of etoricoxib (Garnett, 2001; Tang et al., 2000, 2001). In addition, unlike etoricoxib, a large fraction of the oral dose (~58%) is recovered in feces (Paulson et al., 2000).

Based upon the results of this study, it is concluded that etoricoxib is a low clearance compound (relative to hepatic blood flow), with a  $t_{1/2}$  of 24.8 h. When administered orally, in solution form, etoricoxib is rapidly absorbed ( $T_{max}$  of 1 h), and the extent of absorption is good (~86% as total drug equivalents). The combination of low clearance and good absorption gives rise to an absolute oral bioavailability of ~83% for an oral solution in PEG. In addition, etoricoxib is metabolized extensively (>98%) via 6'-methyl hydroxylation (major) and 1'-N-oxidation. These metabolites are either excreted directly, or are metabolized further to secondary metabolites that are also excreted (urine > feces). Although etoricoxib is cleared by oxidative metabolism, this metabolism is a relatively high  $K_m$  process ( $K_m > 0.1$  mM) in vitro (Kassahun et al., 2001) and, as expected, the pharmacokinetics of etoricoxib are linear over the clinically relevant dose range (Agrawal et al., 2001, 2002). Moreover, the involvement of multiple P450s, and the low first pass effect, effectively minimizes the potential for significant drug interactions with potent P450 inhibitors. In agreement with this hypothesis, ketoconazole, a potent inhibitor of CYP3A4, did not elicit a clinically significant effect on the pharmacokinetics of etoricoxib (N. G. B. Agrawal, unpublished).

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