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Complementary studies of the gastrointestinal safety of the cyclo-oxygenase-2-selective inhibitor etoricoxib

R. H. HUNT*, S. HARPER†, P. CALLEGARI†, C. YU†, H. QUAN†, J. EVANS†, C. JAMES*, B. BOWEN* & F. RASHID*

**McMaster University Medical Center, Hamilton, Ont., Canada; †Merck Research Laboratories, West Point, PA, USA*

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SUMMARY

Background: Cyclo-oxygenase-2-selective non-steroidal anti-inflammatory drugs are intended to preserve cyclo-oxygenase-1-mediated gastroprotection and platelet function, whilst inhibiting cyclo-oxygenase-2-mediated inflammation.

Aim: To assess the gastrointestinal safety of the cyclo-oxygenase-2-selective inhibitor etoricoxib vs. non-selective non-steroidal anti-inflammatory drugs.

Methods: Two randomized, double-blind, placebo- and active-controlled studies were performed: (i) daily faecal red blood cell loss was measured in 62 subjects receiving etoricoxib (120 mg once daily), ibuprofen (800 mg t.d.s.) or placebo for 28 days; (ii) the incidence of endoscopically detectable gastric/duodenal ulcers was determined in 742 osteoarthritis or rheumatoid arthritis patients receiving etoricoxib (120 mg once daily), naproxen (500 mg b.d.) or placebo over 12 weeks.

Results: In the first study, the between-treatment ratio of faecal blood loss for etoricoxib vs. placebo (1.06) was not significantly different from unity; however, the ratios for ibuprofen vs. placebo (3.26) and etoricoxib (3.08) were significantly greater than unity ($P < 0.001$). In the second study, the incidence of ulcers of ≥ 3 mm with naproxen (25.3%) was significantly higher than that with etoricoxib (7.4%) or placebo (1.4%; $P < 0.001$); the results were similar for ulcers of ≥ 5 mm.

Conclusions: The reduced toxicity of etoricoxib (less faecal blood loss and fewer endoscopically detectable lesions) suggests that use of this drug will may be associated with a reduced incidence of gastrointestinal perforations, ulcers and bleeds.

INTRODUCTION

Because gastrointestinal toxicity is the most common serious adverse event associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs),[1] the search for alternative anti-inflammatory agents has focused on reducing the adverse effects on the gastrointestinal tract whilst maintaining efficacy. Previous studies have suggested that the inhibition of cyclo-oxygenase (COX)-mediated prostaglandin synthesis within the gastrointestinal mucosa may play a role in the pathogenesis of NSAID-induced gastrointestinal toxicity.[2–5] Evidence supports the finding that COX-1 is the predominant isoform in the human stomach,[6, 7] and that COX-1 mediates prostaglandin synthesis in the normal human gastric mucosa.[8] It has been postulated that the prostaglandins produced by COX-1 help to protect the gastric and duodenal mucosa by several mechanisms, including the reduction of acid secretion and the stimulation of mucous secretion, bicarbonate secretion, mucosal blood flow and the production of mucosal phospholipids.[9, 10] It has also been suggested that the inhibition of prostaglandin synthesis within the gastric and duodenal mucosa by non-selective NSAIDs may compromise these protective functions, thereby contributing to the pathogenesis of NSAID-induced gastrointestinal toxicity.[11]

Correspondence to: Professor Richard H. Hunt, Division of Gastroenterology, 1200 Main St. West, Room 4WS, McMaster University Medical Center, Hamilton, Ont. L8N 3Z5, Canada.
E-mail: huntr@mcmaster.ca

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The development of COX-2-selective NSAIDs, such as rofecoxib and celecoxib, has provided support for the supposition that the coxibs spare COX-1 and pose a lower risk to the gastrointestinal tract than non-selective NSAIDs. The results of a recent study in healthy subjects showed that faecal red blood cell loss with rofecoxib was significantly less than that observed with a therapeutic dose of the non-selective NSAID ibuprofen and equivalent to that seen with placebo.[12] In addition, two identical endoscopic studies with rofecoxib[13, 14] reported a reduction in the incidence of ulcers over 6 months of approximately 70% when compared with ibuprofen.[15] The rate of endoscopically detectable ulcers seen in studies of celecoxib was also observed to be lower than that found in patients treated with non-selective NSAIDs.[16–18] Furthermore, the results of a prospective, randomized, double-blind comparison of rofecoxib with naproxen in 8076 patients with rheumatoid arthritis (the VIGOR trial) showed an approximately 50% reduction in the incidence of upper gastrointestinal clinical events;[15] similarly, celecoxib was associated with a lower incidence of symptomatic ulcers and ulcer complications combined, in comparison with non-selective NSAIDs (the CLASS study).[19] A reduction of approximately 50% was also reported in the incidence of upper gastrointestinal clinical events with rofecoxib vs. non-selective NSAIDs in a pre-specified, combined analysis of eight double-blind studies that included 5435 patients with osteoarthritis.[20]

Etoricoxib is a new and highly selective COX-2 inhibitor with a long half-life and rapid time to maximum plasma concentration. It is anticipated that the profile of etoricoxib, like that of rofecoxib, will show a reduced incidence of gastrointestinal toxicity in contrast with the profile of non-selective NSAIDs. Therefore, the characterization of its potential for gastrointestinal toxicity has been an important part of the assessment of etoricoxib. Measures of faecal red blood cell loss and direct endoscopic visualization of mucosal lesions provide complementary information about the effects of anti-inflammatory drugs on the gastrointestinal tract. Etoricoxib was studied in both contexts.

The clinical model of faecal blood loss provides a surrogate indirect measure of injury over the entire length of the gastrointestinal tract, including areas beyond the reach of the upper gastrointestinal endoscope. The faecal blood loss study of etoricoxib used a precise technique to measure possible microbleeding throughout the gastrointestinal tract. Subjects underwent re-infusion of ^{51}Cr-labelled erythrocytes, and faecal red blood cell loss was monitored by the determination of the radioactivity contained in the stool.[21] The amount of faecal blood loss correlated well with the endoscopic determination of the erosive gastritis and ulcers caused by gastric irritants.[21–26] Previous experience with non-selective NSAIDs and rofecoxib suggests that the magnitude of drug-induced microbleeding, as measured by faecal blood loss, may be a marker of the potential to cause clinically significant gastrointestinal toxicity.[12, 27]

Gastrointestinal microbleeding assessed by ^{51}Cr-labelled faecal red blood cell loss is one measure of the mucosal damage anywhere from the mouth to the anus, damage which may or may not be accompanied by an endoscopically visible lesion. Endoscopy complements faecal blood loss quantification by providing visualization of oesophageal, gastric or duodenal mucosal lesions; however, this method does not directly assess the platelet-inhibiting activity, and the resultant risk of bleeding, associated with non-selective COX inhibition. Endoscopic monitoring of mucosal integrity can help to determine the frequency of drug-related upper gastrointestinal erosions, ulcers and bleeding.[26] A reduction in gastric and/or duodenal ulcers detected by endoscopic surveillance appears to predict upper gastrointestinal clinical event outcomes.[28] The potential of endoscopy as a predictor of clinical outcome is re-affirmed by the concordance of the results of previous rofecoxib studies.[13–15, 20] In this paper, we present the results of a faecal red blood cell loss study in healthy subjects and an endoscopy study in osteoarthritis and rheumatoid arthritis patients with the new, highly selective, COX-2 inhibitor, etoricoxib. The studies compared a high dose of etoricoxib (twice that anticipated for the chronic treatment of osteoarthritis[29] and equal to that anticipated for the treatment of acute pain[30]) with clinically recommended doses of non-selective NSAIDs. The combination of results from both types of assessment of the gastrointestinal tract provides a stronger characterization of the gastrointestinal safety profile of etoricoxib than either study would provide independently.

METHODS

All subjects or patients participating in the studies gave written informed consent, and both studies were

conducted in conformance with applicable national or local ethical requirements.

Faecal red blood cell loss study

Faecal red blood cell loss with etoricoxib was evaluated as described in a previously published randomized, double-blind study of the COX-2-selective inhibitor rofecoxib.[12] Sixty-two healthy male subjects between 19 and 33 years of age, with a history of regular bowel habits of at least one stool per day, were enrolled by the investigator in this single-centre, parallel-group, randomized, double-blind, active- and placebo-controlled study. The study began in November 1999 and ended in April 2000.

Subjects were re-injected with their own ^{51}Cr-labelled red blood cells, and daily faecal blood loss in the total collected stool sample was measured using a large sample counter. Subjects with normal faecal blood loss during a 1-week, placebo, single-blind, baseline period were randomized to receive oral etoricoxib (120 mg once daily), which is twice the dose anticipated for chronic use in osteoarthritis patients,[29] oral ibuprofen (800 mg three times daily) or placebo for 28 days. Randomization was performed according to an allocation schedule generated by computer at Merck Research Laboratories. Treatments for each subject were packaged in numbered containers.

The primary end-point was the ratio of the average daily faecal blood loss (mL/day) for weeks 2–4 of active treatment to the pre-treatment baseline faecal blood loss. The second to fourth weeks of drug treatment were pre-determined for analysis, in order to exclude the possibility that acute ibuprofen-induced mucosal injury in the first week might increase the apparent rate of blood loss in this group. The ratio was calculated for each subject and comparisons were made between treatments. Safety was evaluated by physical examinations, laboratory parameters, electrocardiograms and adverse events.

Analysis of covariance was used to analyse the logarithm of the treatment-to-baseline ratio for the comparison of treatment effects. The 95% confidence interval (CI) was calculated for the between-group ratio of the treatment-to-baseline least-squares geometric mean ratios to compare the effects of study therapy on average daily faecal blood loss. For the comparison of etoricoxib with placebo, a conservative similarity bound of 1.7 was pre-specified as the upper limit of the 95% CI.

Endoscopy study in osteoarthritis and rheumatoid arthritis patients

A multicentre, multinational, randomized, double-blind, parallel-group, active comparator and placebo-controlled study was performed from December 1999 to November 2000 to determine the incidence of gastric and/or duodenal ulcers in patients with osteoarthritis or rheumatoid arthritis over 12 weeks of treatment with etoricoxib, naproxen or placebo. Seven hundred and forty-two patients (130 males, 612 females) between the ages of 18 and 83 years were enrolled. Patients were excluded if they had an oesophageal, gastric or duodenal ulcer, pyloric obstruction or erosive oesophagitis at baseline endoscopy. The study population included patients infected with *Helicobacter pylori* and those with risk factors for the development of gastric or duodenal ulcers with non-selective NSAIDs, including age $\geq$ 65 years, a previous history of a gastroduodenal event (e.g. perforation, ulcer or bleed), use of corticosteroids and/or low-dose aspirin and the presence of gastroduodenal erosions at baseline.[1, 31–33] Patient baseline characteristics are shown in Table 1. Following a 2-week washout period from non-selective NSAIDs, gastroprotective agents (including proton pump inhibitors, H_2-receptor antagonists, prostaglandin analogues or other protective agents such as sucralfate) and antibiotics, patients underwent baseline endoscopy and the determination of *H. pylori* status.

A randomization schedule generated by computer at Merck Research Laboratories was used to assign patients to one of three treatment groups: etoricoxib, 120 mg once daily ($n = 251$), naproxen, 500 mg twice daily ($n = 244$), or placebo ($n = 247$). Within each study site, allocation was stratified by positive or negative history of significant upper gastrointestinal disease (i.e. event), and secondarily by the use of low-dose aspirin. Study medication was provided in numbered containers.

The concurrent use of oral corticosteroid ($\leq$ 10 mg prednisone equivalent daily) and low-dose aspirin ($\leq$ 100 mg daily) was permitted, and rescue medications [acetaminophen for pain and Gelusil (aluminium hydroxide/magnesium hydroxide/simethicone, Warner-Lambert) for minor dyspepsia] were provided.

Patients were evaluated clinically at study weeks 3, 6, 9 and 12. Endoscopy was performed at baseline, at study weeks 6 and 12, and at any unscheduled discontinuation or when deemed clinically necessary by the

Table 1. Endoscopy study: patient baseline characteristics

	Placebo	Etoricoxib (120 mg)	Naproxen (1000 mg)
Randomized patients (*n*)	247	251	244
Female (%)	81	84	83
Mean age (years)	54	53	54
Age range (years)	22–83	18–79	18–80
Age ≥ 65 years (%)	23	18	22
Caucasian (%)	57	57	57
Black (%)	4	7	6
Hispanic (%)	21	19	20
Osteoarthritis (%)	24	27	23
Rheumatoid arthritis (%)	76	73	77
Positive gastrointestinal history (%)	9	10	9
Positive *Helicobacter pylori* status* (%)	60	51	58
Patients with gastroduodenal erosions present at baseline endoscopy (%)	14	13	17
Tobacco use (%)	45	46	41
Previous NSAID use (%)	72	74	77
Corticosteroid use (%)	39	37	37
Low-dose aspirin use (≤ 100 mg daily) (%)	4	4	5

NSAID, non-steroidal anti-inflammatory drug.
* Determined by urease test (CLO test) or histopathology results on gastric biopsy samples taken at baseline endoscopy.

investigator. At each endoscopy, the number and size of gastric and/or duodenal ulcers (defined as a mucosal break with unequivocal depth) of at least 3 mm in the longest dimension were recorded, and gastroduodenal mucosal erosions (defined as a mucosal break of any size with no depth) were also counted. If an ulcer was detected at either week 6 or 12, the patient was immediately discontinued from the study and underwent discontinuation procedures and ulcer treatment. Assessments also included physical examination and vital signs, laboratory parameters and the monitoring of adverse events.

The primary end-point of the study was the cumulative incidence of gastric and/or duodenal ulcers (≥ 3 mm) measured at weeks 6 and 12, with a secondary end-point of the cumulative incidence of larger ulcers (≥ 5 mm) over 12 weeks. Gastroduodenal erosions were included as exploratory end-points. The study had a 98% power to detect a difference in the 12-week cumulative incidence rate of patients who developed gastric and/or duodenal ulcers between naproxen and etoricoxib or placebo, based on a two-sided test with $\alpha = 0.05$ between treatment groups. These estimates assumed that the true incidence rates were 7.5% for etoricoxib, 7.5% for placebo and 25% for naproxen.

The log-rank test was used to compare the cumulative incidence between treatment groups, and a life-table (survival) analysis was used to analyse time to event data for ulcer incidence. Ninety-five per cent CIs were calculated for the between-treatment difference and ratio of the 12-week cumulative life-table rates. Twelve-week cumulative life-table rates were based on Kaplan–Meier estimates and the CIs were calculated using the Breslow–Crowley method.[34] An analysis of covariance model with pre-specified factors (treatment, gastrointestinal history and baseline covariate where appropriate) was used to analyse continuous variables.

RESULTS

Faecal blood loss study in healthy subjects

Figure 1 shows the disposition of volunteers in the study; three subjects were withdrawn from the study prior to unblinding due to infection with pinworm, the effects of which on faecal red blood cell loss were unknown. As shown in Figure 2, faecal blood loss increased consistently throughout the study with ibuprofen (800 mg three times daily), whereas faecal blood loss in subjects taking daily etoricoxib (120 mg) did not differ from that seen with placebo. As expected in this model, faecal blood loss also increased slightly in the placebo group over the course of the study. The least-squares geometric mean ratio of weeks 2–4/baseline

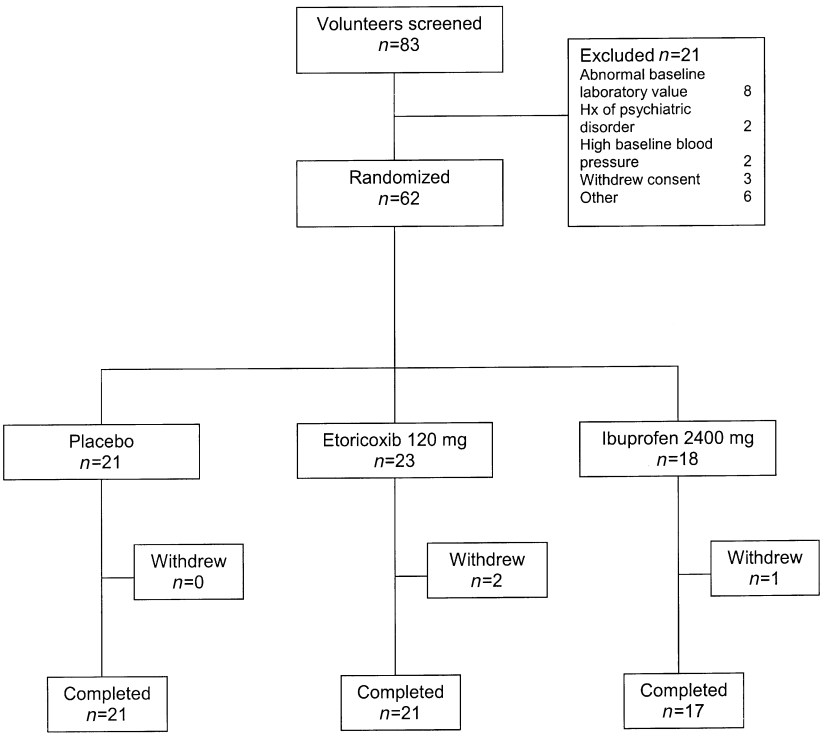

Figure 1. Flow chart of faecal red blood cell loss study.

faecal blood loss was 2.44 in the placebo group, 2.59 in the etoricoxib (120 mg) group and 7.97 in the ibuprofen (2400 mg) group. The between-treatment ratio for the etoricoxib (120 mg) group vs. placebo (1.06; 95% CI: 0.84, 1.34) was not significantly different from unity ($P = 0.630$), and the upper bound of the 95% CI was smaller than the pre-specified comparability bound of 1.7. By contrast, the between-treatment ratios of ibuprofen vs. placebo (3.26; 95% CI: 2.55, 44.17) and ibuprofen vs. etoricoxib (3.08; 95% CI: 2.41, 3.94) were significantly greater than unity ($P < 0.001$).

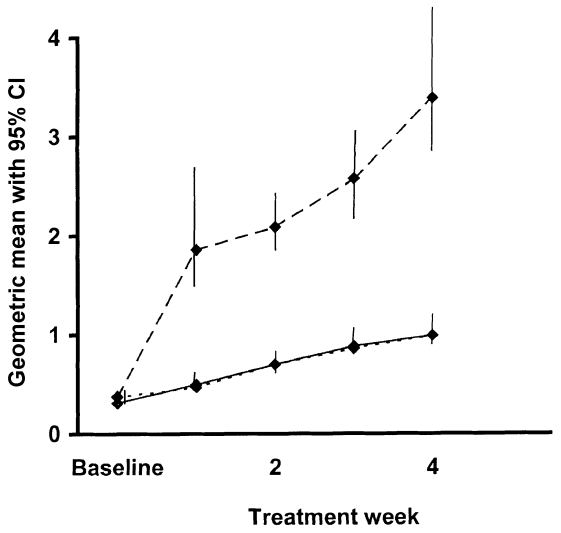

Figure 2. Mean daily faecal blood loss over 4 weeks. Narrow broken line, placebo ($n = 21$). Wide broken line, ibuprofen (2400 mg) ($n = 18$). Full line, etoricoxib (120 mg) ($n = 23$). CI, confidence interval.

There were no serious adverse experiences, and no subjects were discontinued because of adverse events. Clinical and laboratory adverse events were tabulated but, due to the small sample size, no formal statistical analysis was performed to compare treatment effects on safety parameters. Etoricoxib was generally well tolerated.

Endoscopy study in osteoarthritis and rheumatoid arthritis patients

Figure 3 shows the disposition of patients throughout the study. The incidence of gastric and/or duodenal ulcers of ≥ 3 mm (Figure 4) at 12 weeks in the naproxen group was significantly higher than that in the etoricoxib group [difference (95% CI), 17.85% (11.20%, 24.50%); $P < 0.001$] and placebo group [difference (95% CI), 23.92% (18.01%, 29.83%); $P < 0.001$]. The findings for ulcers of ≥ 5 mm were similar [naproxen vs. etoricoxib: difference (95% CI), 12.72% (6.58%,

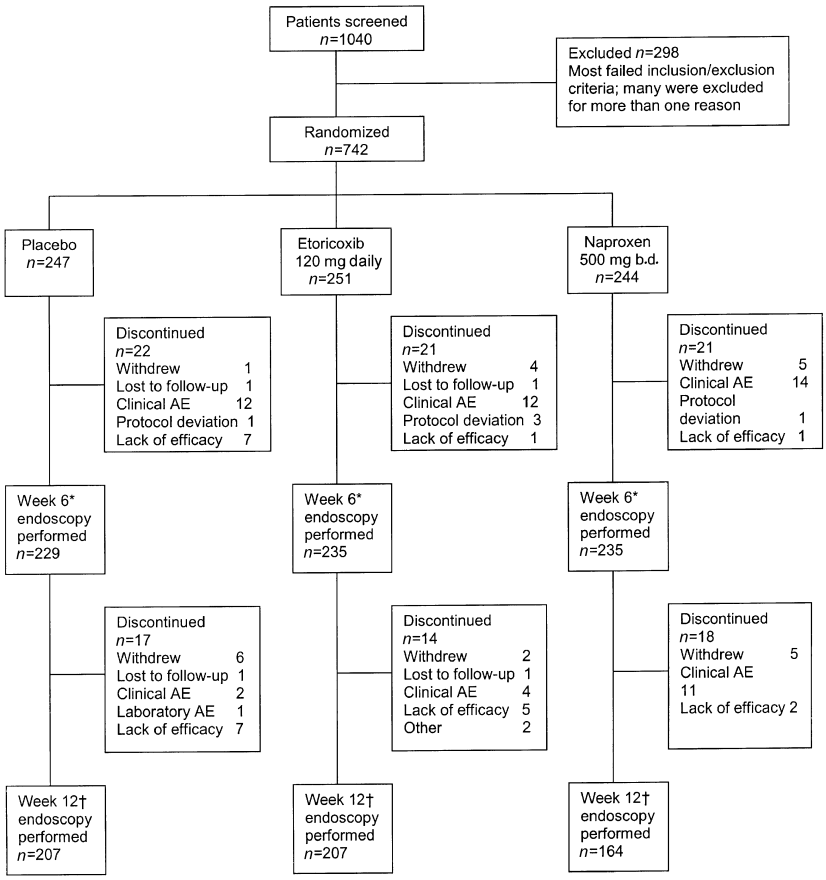

Figure 3. Flow chart of endoscopy study. *Endoscopies performed up to week 6 including those for patients who discontinued. †Endoscopies performed from weeks 6 to 12 including those for patients who discontinued. AE, adverse event.

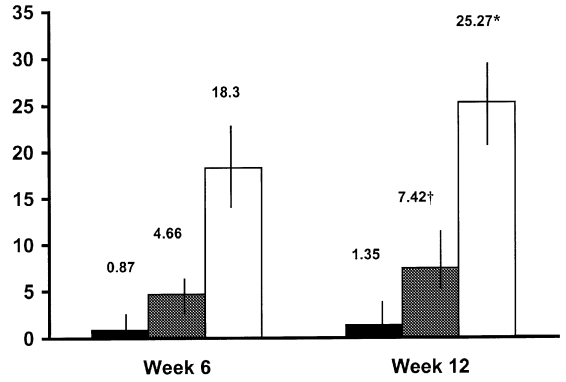

Figure 4. Life-table cumulative incidence of gastroduodenal ulcers of ≥ 3 mm with 95% confidence interval (intention-to-treat). Filled bar, placebo. Shaded bar, etoricoxib (120 mg). Open bar, naproxen (1000 mg). *$P < 0.001$ for naproxen vs. etoricoxib or placebo. †$P = 0.002$ for etoricoxib vs. placebo; not pre-specified.

18.85%); $P < 0.001$; naproxen vs. placebo: difference (95% CI), 18.37% (12.99%, 23.74%); $P < 0.001$]. Based on the endoscopically observed ulcer incidence at 12 weeks, six patients would need to be treated with etoricoxib (120 mg) rather than with naproxen (1000 mg) to avert the development of an ulcer in one patient. Although not a pre-specified comparison, the incidence of ulcers in the etoricoxib group was significantly higher than that in the placebo group (for ulcers of ≥ 3 mm: 7.42% vs. 1.35%; $P = 0.002$; for ulcers of ≥ 5 mm: 6.57% vs. 0.92%; $P = 0.002$).

Ulcer (≥ 3 mm) incidence in the subgroups defined by baseline patient characteristics was generally qualitatively consistent across the subgroups. The presence of gastric or duodenal mucosal erosions at baseline was a significant risk factor for ulcers ($P = 0.048$).

The change in the number of erosions from baseline to week 12 is shown in Figure 5. The analysis of gastroduodenal erosions at 12 weeks showed a significantly lower mean change from baseline for etoricoxib vs. naproxen [difference (95% CI), 3.54 (2.95, 4.13); $P < 0.001$] and for placebo vs. naproxen [difference (95% CI), 3.56 (2.96, 4.15); $P < 0.001$]. Although not a pre-specified comparison, no significant difference was observed between the etoricoxib and placebo groups in the mean change from the baseline number of erosions [difference (95% CI), 0.02 (− 0.58, 0.61);

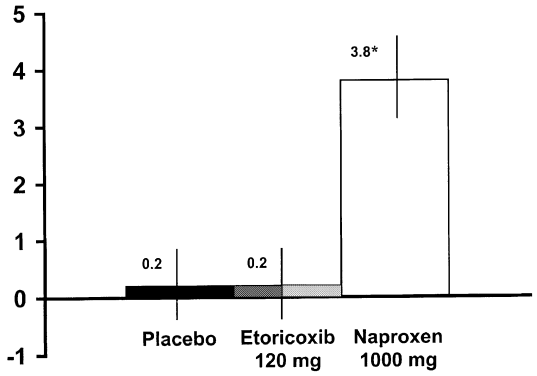

Figure 5. Change in the number of gastroduodenal erosions (95% confidence interval) from baseline to week 12. *$P < 0.001$ for naproxen vs. placebo or etoricoxib.

$P = 0.957$; Figure 5] or in the incidence of the increase in erosions [difference (95% CI), −0.53 (− 8.38, 7.32); $P = 0.898$].

Exploratory analyses of the incidence of gastric and duodenal ulcers were performed separately. Results for gastric ulcer were consistent with those of the combined gastric and duodenal results. The number of patients with duodenal ulcer was small in all of the three treatment groups, and the incidence rates for duodenal ulcer were lower than those for gastric ulcer. The relative ordering of the rates by treatment for duodenal ulcer was similar to that for gastric ulcer.

The rates of discontinuation due to clinical adverse events were similar across the treatment groups: 5.7% for placebo, 6.4% for etoricoxib and 10.2% for naproxen. The incidence of drug-related adverse events in the naproxen group (37.7%) was significantly higher than that for placebo (21.9%, $P < 0.001$), whereas the incidence for the etoricoxib group (27.5%) was not significantly different from that for placebo ($P = 0.148$). The proportions of patients who discontinued due to a digestive system adverse experience or abdominal pain were 0.4% for placebo, 4.0% for etoricoxib and 9.0% for naproxen ($P \leq 0.011$ for etoricoxib or naproxen vs. placebo). The overall incidence of laboratory adverse experiences was similar across all treatment groups (13.1%, 10.8% and 10.7% in the placebo, etoricoxib and naproxen groups, respectively).

Because the potential risks of COX-2 inhibition include a subset of the known mechanism-based adverse effects of non-selective NSAIDs, particular attention was paid to renal-related adverse events, such as hypertension or oedema. In the present study, the incidence rates of lower extremity oedema were 2.0% in the naproxen group, 1.6% in the placebo group and 1.6% in the etoricoxib group, and no patient in the trial discontinued due to oedema. The incidence of hypertension was also similar in the three treatment groups (2.4%, 2.0% and 2.9% in the placebo, etoricoxib and naproxen groups, respectively), as was the discontinuation rate for hypertension [one patient in the etoricoxib (120 mg) group discontinued due to hypertension, which was considered to be definitely not related to the study drug by the investigator]. No patient experienced congestive heart failure, pulmonary oedema or cardiac failure.

DISCUSSION

The results of these two gastrointestinal tolerability studies provide complementary evidence that the highly selective COX-2 inhibitor etoricoxib has reduced gastrointestinal toxicity compared with non-selective NSAIDs. Faecal red blood cell loss with etoricoxib (120 mg) (twice the dose similar in efficacy to the dose of ibuprofen studied[29]) was significantly less than that with ibuprofen and was equivalent to that with placebo in healthy volunteers. Etoricoxib also resulted in a significantly lower incidence of endoscopically detectable ulcers and erosions than the non-selective NSAID comparator naproxen over a 12-week treatment period; these findings are consistent with the results of a combined analysis of 10 Phase II/III trials, which have shown that treatment with etoricoxib reduces the incidence of investigator-reported and confirmed upper gastrointestinal events by approximately 50% compared with treatment with non-selective NSAIDs,[35] and similar to the results seen with rofecoxib.[15] In addition, the safety results of the present studies support the generally good tolerability of etoricoxib in patients with osteoarthritis or rheumatoid arthritis.

The etoricoxib faecal blood loss study results are consistent with a COX-1 sparing effect of etoricoxib (120 mg once daily) similar to that of placebo. COX-1 inhibition would be expected to cause a combination of mucosal injury and platelet dysfunction, leading to gastrointestinal microbleeding, for which the faecal blood loss study is extremely sensitive; consistent with this expectation, the non-selective COX inhibitor ibuprofen (800 mg three times daily) increased the faecal red blood cell loss compared with placebo. The placebo effect observed in this study (2.4 times that of baseline) was similar to the results reported in previous studies.[12, 36]

The results of the endoscopy study in osteoarthritis/rheumatoid arthritis patients support the findings from the faecal blood loss study in healthy volunteers. Treatment with etoricoxib resulted in significantly fewer ulcers and erosions than did treatment with naproxen; only six patients would need to be treated with etoricoxib vs. naproxen in order to avert the development of ulcers in one patient. Etoricoxib was similar to placebo in terms of the incidence of erosions, although there was a higher incidence of ulcers in patients taking etoricoxib relative to placebo. Unlike the findings for etoricoxib in this study, the results for the naproxen group showed an increased incidence of both ulcers and erosions, as has been observed in previous studies with oral or parenteral non-selective NSAIDs.[13, 14, 37, 38]

Several possible reasons could account for the observed difference in ulcer incidence between etoricoxib and placebo. Local topical effects of etoricoxib, whether mediated by COX inhibition or other chemical effects, appear to be unlikely. The number of gastric or duodenal erosions seen with etoricoxib was similar to that seen with placebo, suggesting that etoricoxib did not have a direct topical effect on the gastrointestinal mucosa. Considerable evidence also suggests that systemic COX-1 inhibition is unlikely. For example, at single doses up to 250 mg and multiple doses up to 150 mg daily, etoricoxib caused no significant inhibition of COX-1 when compared with placebo in assays of platelet function and assays of prostanoid production by human whole blood in healthy subjects.[39] Moreover, a multiple-dose study in healthy subjects to assess the effects of etoricoxib on *ex vivo* prostaglandin synthesis in gastric biopsy samples demonstrated that etoricoxib (120 mg taken once daily) had no effect on prostaglandin E_2 synthesis and was not statistically different from placebo in gastric biopsy tissue.[40] These results, together with those of the faecal blood loss study described here, clearly support the COX-2 selectivity of etoricoxib.

A consideration of the mechanisms of healing of mucosal injury suggests another interpretation of the findings in the present endoscopy study. Studies in animal models with both non-selective NSAIDs and selective COX-2 inhibitors have demonstrated a role for COX-2 in ulcer healing,[41–43] and COX-2 is expressed in human gastric ulcers[44] where it may play a role in angiogenesis in the ulcer bed.[45] The higher incidence of ulcers seen with etoricoxib (120 mg), a dose higher than that anticipated for chronic use, compared with the placebo group in this study is therefore consistent with the current knowledge about the potential effects of very high levels of COX-2 inhibition on ulcer healing mechanisms. Erosions, by contrast, appear to undergo healing by a process of rapid restitution, in which epithelial cells at the margins of the erosion migrate over the area of compromised mucosa, thereby repairing the defect;[46–50] therefore, COX-2-dependent processes, such as angiogenesis, required for the repair of deeper structures such as ulcers, are not an issue in the healing of erosions. Thus, COX-2 inhibition may slow the healing of ulcers without affecting the healing of superficial mucosal erosions to the same extent, consistent with the findings in the present study.

Another interesting finding in the endoscopy study was that the ulcer incidence rate in the placebo group (1.35%) was lower than the expected estimate of 7.5%.[13, 14] The subsequent widespread availability of marketed COX-2-selective inhibitors may have caused a significant change in clinical practice, such that patients with a higher baseline risk for ulcer may already be committed to therapy with a COX-2-selective NSAID. Such changes in baseline patient characteristics have important implications for the planning and interpretation of future studies in this area.

In conclusion, by assessing injury to the gastrointestinal tract in two different and complementary ways, the faecal red blood cell loss and endoscopy studies reported here provide consistent evidence of the superiority of etoricoxib (120 mg) over non-selective NSAIDs in the preservation of gastrointestinal mucosal integrity and platelet function. These results are also consistent with the similarity in the reduction of risk for gastrointestinal clinical events between rofecoxib and etoricoxib,[15, 20] as gastrointestinal clinical event analysis is influenced by the presence or absence of platelet-inhibiting activity due to COX-1 inhibition. Taken together, these results confirm the hypothesis that treatment with etoricoxib confers less risk of the development of the clinical manifestations of gastrointestinal toxicity typically seen with non-selective NSAIDs. By supporting the concept that sparing COX-1 results in a lack of interference with platelet function and gastroprotective mechanisms, the complementary findings of less gastrointestinal bleeding and fewer endoscopically detectable mucosal lesions confirm the premise that COX-2-selective inhibitors pose less risk of gastrotoxicity than do non-selective NSAIDs.

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