



PharmaNote®

VOLUME 20, ISSUE 3

DECEMBER 2004

ETORICOXIB: A NEW COX-2 INHIBITOR

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been widely used to treat pain, inflammation and fever. NSAIDs exert their effects by inhibiting the cyclooxygenase enzyme (COX), which exists in two isoforms, COX-1 and COX-2. COX-1 is responsible for the propagation of gastric cytoprotective products, while COX-2 fosters the production of compounds that contribute to inflammation, pain and fever. Recent research has focused on COX-2-specific analgesics that might spare the gastric mucosa while eliciting anti-inflammatory and analgesic actions. The FDA has approved three COX-2-specific NSAIDs: celecoxib (Celebrex™), rofecoxib (Vioxx™), and valdecoxib (Bextra™). Rofecoxib was voluntarily withdrawn from the Market by Merck on September 30, 2004 due to concerns regarding its cardiovascular safety. Merck is in the process of acquiring approval for a new COX-2 inhibitor, etoricoxib (Arcoxia™) with indications for rheumatoid and osteoarthritis, chronic low back pain, acute pain, dysmenorrhea, acute gouty arthritis, and ankylosing spondylitis. Currently Arcoxia™ is approved and marketed in 45 countries worldwide, including Latin America, Europe, and the Asian-Pacific region. The FDA is

currently reviewing the New Drug Application (NDA) for etoricoxib.¹

This paper will present the current evidence of etoricoxib's efficacy and safety.

Pharmacology and Pharmacokinetics

Prostaglandins (PGs) play a vital role in the development of inflammation, pain, and fever by stimulating inflammatory cell chemotaxis, amplifying the formation of pain impulses and causing vasodilatation. PGs signal the hypothalamus to increase the body's temperature in response to bacterial toxins and other pyrogens. PGs are produced when COX catalyzes their production from arachidonic acid. All NSAIDs decrease PG production by inhibiting the COX enzyme system. Selective inhibitors block primarily COX-2, while non-selective agents inhibit both COX-1 and COX-2 enzymes. COX-1 produces PGs that are cytoprotective to the gastrointestinal (GI) tract, but also forms thromboxane A₂ in platelets, leading to vasoconstriction and platelet aggregation. COX-2 is usually found in smaller concentrations in the body, but can be induced by cytokines, endotoxins, and tumor promoters resulting in signs and symptoms of inflammation, pain and fever.² Non-selective

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Table 1. IC₅₀ values for the inhibition of COX-1 and COX-2¹⁴

Drug	IC ₅₀ COX-1 (μM)	IC ₅₀ COX-2 (μM)	COX-2:COX-1 Ratio (Selectivity)
Etoricoxib	116.00	1.10	106.00
Rofecoxib (removed from market 9/04)	18.80	0.53	35.00
Valdecoxib	26.10	0.87	30.00
Celecoxib	26.10	0.87	7.60
Diclofenac	0.15	0.05	3.00
Etodolac	9.00	3.70	2.40
Meloxicam	1.40	0.70	2.00
Indomethacin	0.19	0.44	0.40
Ibuprofen	4.80	24.30	0.20
Piroxicam	0.76	9.00	0.08

*Experiment performed as whole blood assay. IC₅₀= concentration required for 50% inhibition.

NSAIDs have been available for many years, but they must be used with caution in patients at risk for gastrointestinal (GI) bleeding, such as the elderly, those with a history of GI bleeding, or concomitant use of anticoagulants, corticosteroids or aspirin.

COX-2-specific inhibitors relieve inflammation, pain and fever while decreasing the risk of gastrointestinal (GI) complications. Though “selective,” they still retain dose-dependent COX-1 inhibition, which is defined by their COX-1/COX-2 ratio. (Table 1)

Etoricoxib is well absorbed with an average absolute bioavailability of 83% (70-99%), and a peak plasma concentration of 1.36 mcg/mol reached within 1 hour of oral administration. The half-life of etoricoxib is 24.8 hours. Hepatic extraction appears to be very low (approximately 4%), contributing to negligible first pass metabolism. Etoricoxib is extensively metabolized (>98%), primarily by 6'-methyl hydroxylation. Metabolism is predominantly to a 6'-carboxylic acid and to an O-β-D-glucuronide conjugate. The carboxylic acid metabolite is the major renally- and fecally-excreted metabolite, approximately 80% and 67%, respectively. The glucuronide appears to be excreted into the bile and further hydrolyzed by gut bacteria. Hepatic metabolism involves multiple cytochrome P450 (CYP) enzymes, with CYP3A4 accounting for approximately 60%. However, ketoconazole, a potent CYP3A4 inhibitor, did not result in a clinically significant effect on the pharmacokinetics of etoricoxib.³

The pharmacokinetics of etoricoxib appear to be linear. The area under the curve rises in pro-

portion to increased doses from 5 to 120 mg. Agrawal et al.⁴ studied the pharmacokinetics while administering etoricoxib with water alone after a small fast with no serious clinical adverse events, and no side effects that caused discontinuation. Further study in the fed state is needed to elucidate the effect of food on etoricoxib's pharmacokinetics.

In patients with mild hepatic insufficiency (Child-Pugh score of 5 to 6) a 60 mg once-daily dose of etoricoxib is suggested. In moderate hepatic insufficiency (Child-Pugh score of 7 to 9), a 60 mg every-other-day dosing regimen is recommended. Absorption does not appear to be affected by hepatic impairment. Currently no dosing recommendations are available for severe hepatic insufficiency.⁵

Preclinical trials have indicated that etoricoxib significantly inhibited the production of lipopolysaccharide (LPS)-stimulated-PGE₂ (a surrogate for COX-2 activity), but did not significantly inhibit gastric PGE₂ synthesis. Dallob and colleagues found that 500 mg of etoricoxib (more than 3 times the therapeutic dose) did not significantly effect the production of TXB₂ (a surrogate for COX-1 activity) or inhibit the antiplatelet effects of low-dose aspirin.⁶ Furthermore, at multiple daily doses of up to 150 mg, etoricoxib had no effect on bleeding time.

Clinical Trials

Analgesia

The Dental Impaction Pain Model was used by Malmstrom et al.⁷ to compare pain relief between placebo, etoricoxib 120 mg, naproxen so-

dium 550 mg, and acetaminophen/codeine 600/60 mg. Total pain relief score over 8 hours (TOPAR8) was calculated (higher TOPAR8 scores indicate greater pain relief). Etoricoxib (20.9 [18.5, 23.3]) and naproxen (21.3 [19.0, 23.7]) were significantly more effective than acetaminophen/codeine (11.5 [9.1, 13.8]), $p = <0.001$. All active treatment groups relieved pain significantly more than placebo; there was no significant difference between etoricoxib and naproxen. One hour after the dose, all medication groups showed improved pain relief versus placebo. The onset of pain relief was approximately 30 minutes for all drug treatment groups. Rescue medications were given if patients required extra pain relief. Over the 24-hour follow-up period, 90%, 44%, 52.9%, and 76% of patients took rescue medication in the placebo, etoricoxib, naproxen sodium and acetaminophen/codeine groups, respectively. The time-to-rescue-medication was significantly longer in patients taking etoricoxib than in placebo- or acetaminophen/codeine-treated patients (>24 hours, 1.6 hours, 3.6 hours, respectively, $p < 0.001$). Time-to-rescue medication was similar for etoricoxib and naproxen. Clinical adverse events occurred in 36%, 26%, 37%, and 50% for the placebo, etoricoxib, naproxen sodium, and acetaminophen/codeine groups, respectively. The most common complaints were nausea, post-extraction alveolitis, and headache; headache occurred less frequently in the etoricoxib group compared to other treatment groups. In this model, etoricoxib appears to have equivalent efficacy compared to naproxen for relieving acute, moderate to severe pain.

Acute Gout

Rubin et al.⁸ conducted a randomized, controlled, double blind, active comparator versus placebo-controlled study to investigate the effectiveness of etoricoxib in acute gout. A once-daily 120 mg dose of etoricoxib was compared to a indomethacin 50 mg three-times daily, and placebo. Based on a 5-point pain score with increasing values representing increased pain, the decrease in joint pain over days 2-5 of treatment was comparable in the etoricoxib and indomethacin groups, -1.79 (95% CI -1.95, -1.63) and -1.71 (95% CI -1.88, -1.54), respectively. Differences between the two medications were not significant ($p = 0.46$).

These results remained comparable after 8 days of treatment. No significant difference was noted between the two medications ($p = 0.52$), nor was the global assessment significantly different ($p = 0.43$). Patients appeared to get equal relief of pain from etoricoxib or indomethacin. Drug-related adverse effects were significantly lower in the etoricoxib group (16.5%) compared to the indomethacin group (37.2%), $p = 0.002$. Twice as many patients taking indomethacin (20.9%) experienced GI adverse effects compared with etoricoxib (9.7%), yet none of these were serious enough to discontinue therapy. Etoricoxib 120 mg once-daily is as effective as indomethacin 50 mg three times daily, and appears to have fewer adverse effects.

Osteoarthritis and Rheumatoid Arthritis

Zacher et al.⁹ conducted a 6-week double-blind, active comparator-controlled parallel-group study comparing the efficacy, safety and tolerability of 60 mg of etoricoxib once daily with diclofenac 50 mg three times daily in patients with osteoarthritis. Etoricoxib and diclofenac were comparable in reducing pain as per a patient reported pain scale. Pain relief was similar between the etoricoxib (-31.3 [-33.6, -29.0]) and diclofenac (-30.9 [-33.2, -28.6]) groups over the 6-week period. No significant difference was noted between the groups. The number of patients who reported an excellent response to therapy at 4 hours post-dose on the first day of treatment via 5-point Likert scale (0 = excellent, 4 = no response) was significantly higher in etoricoxib-treated patients: 31.5% (24.96, 38.73) for etoricoxib versus 19.1% (13.88, 25.25) for diclofenac. The 12.4% difference between the two drugs was statistically significant (CI 3.84, 21.07; $p = 0.007$), illustrating etoricoxib's rapid onset of action compared to diclofenac. The incidence of NSAID-related GI adverse events, lower extremity edema, and hypertension was similar. Less than 1% of patients in either group had to discontinue treatment due to these effects. Increases in AST and ALT enzymes were significantly higher in the diclofenac group: 11% and 24% (AST and ALT, respectively), while patients treated with etoricoxib showed no increases in liver enzymes. Drug-related abnormal laboratory values assessed by routine blood chemistries, hematology and urine analyses, were significantly less with etoricoxib (2.7%) com-

Table 2. Adverse events occurring in >1% of patients treated with etoricoxib.

	Etoricoxib			Placebo
	60 mg	90 mg	120 mg	
Digestive				
Diarrhea ¹¹	3.9%	8.4%		1.8%
Nausea ^{11,12}	5.8%	7.5%	3.0%	2.8%
Gast/Duod Ulcers \geq 3mm ¹³			8.1%	1.9%
Respiratory				
Respiratory Tract Infections ¹¹	5.8%	2.8%		6.4%
Central Nervous System				
Dizziness ⁷			2.0%	6.0%
Somnolence ⁷			4.0%	0.0%
Miscellaneous				
Headaches ¹¹	11.7%	5.6%		5.5%

pared to diclofenac (7.3%), $p = 0.025$. Based on these results, once daily 60 mg etoricoxib is as effective as diclofenac 50 mg three times daily for osteoarthritis with fewer patients exhibiting increased AST, ALT, and abnormal lab values.

When Collantes et al.¹⁰ studied etoricoxib in rheumatoid arthritis, the findings resembled those in patients with osteoarthritis. Etoricoxib administered at a dose of 90 mg once daily was found to be comparable to naproxen 500 mg twice-daily during a 12-week follow-up period. Both groups experienced significant improvements compared with placebo in all efficacy endpoints ($p < 0.05$). Both naproxen and etoricoxib were well tolerated.

Chronic Low Back Pain

Birbara et al.¹¹ performed a randomized, placebo-controlled, parallel-group, 12-week, double-blind, phase III study to evaluate the efficacy, safety, and tolerability of etoricoxib in treating chronic lower back pain. Once daily doses of 60 and 90 mg were studied. Both doses showed significant improvement in low back pain intensity after 4 weeks of treatment compared with placebo (60 mg vs. placebo: -12.94 [95% CI -19.03, -6.86] and 90 mg vs placebo: -10.29[-16.26, -4.31]). Similar results were seen over the entire 12-week study. No significant differences were noted between the two doses of etoricoxib. Rescue doses of acetaminophen were offered to every subject. Similar numbers of patients utilized rescue treatment. No

significant differences in clinical adverse events was found between the placebo, 60 mg etoricoxib, and the 90 mg etoricoxib treatment groups: 46.8%, 58.3%, and 52.3%, respectively. The most frequently reported events were headache, nausea, diarrhea, and upper respiratory tract infections. The 90 mg dose of etoricoxib was associated with a higher incidence of drug-related adverse events compared to placebo (27.1% vs. 11.9%, $p = 0.006$), while the 60 mg dose was similar to placebo (20.7% vs. 11.9%, $p = 0.133$). No significant difference in drug-related adverse events (as determined by the investigator) resulting in discontinuation of therapy was noted between placebo (4.6%), 60 mg (7.8%), and 90 mg (9.3%), although such events were numerically higher the active treatment groups. Etoricoxib is effective for treating chronic lower back pain. Thus, the 90 mg dose was no more effective than 60 mg, but it was associated with more drug-related adverse events in this population.

Dysmenorrhea

Etoricoxib 120 mg administered once daily was compared to 550 mg of naproxen sodium or placebo for acute onset dysmenorrhea. Pain relief scores over 8 hours were higher for both etoricoxib (20.0) and naproxen (21.5) versus placebo (12.6), $p < 0.001$, but no significant difference was noted between the two active treatments ($p = 0.326$). Time-to-onset of action and duration of analgesia were significantly better than placebo and similar for

etoricoxib and naproxen. No serious adverse events occurred. The incidence of clinical adverse experiences were 15%, 12%, and 25% for placebo, etoricoxib, and naproxen, respectively. Headache and nausea were the most frequently reported events. The authors concluded that etoricoxib was as effective as naproxen sodium for treating dysmenorrhea, while exhibiting similar safety to placebo and greater safety compared to naproxen in this population.¹²

Dosing and Administration

Etoricoxib is effective for each of the following indications at the respective doses: osteoarthritis, 60 mg;⁹ rheumatoid arthritis, 90 mg;¹⁰ chronic low back pain, 60-90 mg;¹¹ acute pain, 120 mg;⁷ gout, 120 mg;⁸ and primary dysmenorrhea, 120 mg.¹² Given the extended half-life, once daily administration is sufficient. In mild hepatic dysfunction, doses of 60 mg daily are suggested, and in moderate hepatic impairment a dose of 60 mg every other day is recommended.⁷

Further studies need to be conducted to investigate dosing in renal impairment and the elderly. The effect of co-administration of food should also be addressed in future studies.

Toxicity and Safety

Hunt et al.¹³ performed a 12 week, multicenter, multinational, randomized, double-blind, parallel-group, active comparator- and placebo-controlled study to investigate the incidence of gastric and/or duodenal ulcers with the use of 120 mg once-daily etoricoxib, 2400 mg of ibuprofen (800 mg three times daily), and placebo. Aspirin use was permitted (≤ 100 mg daily). Ibuprofen produced significantly more gastric and/or duodenal ulcers ≥ 3 mm (17.02%) than etoricoxib (8.12%) or placebo (1.86%). Ibuprofen, etoricoxib, and placebo resulted in ulcers >5 mm at a rate of 12.32%, 6.18%, and 0.45%, respectively. The difference between etoricoxib and ibuprofen was significant (6.14%; 95% CI 0.63, 11.65; $p = 0.035$). In contrast, overall adverse effects occurred at a similar rate with ibuprofen, etoricoxib, and placebo: 58.0%, 56.6%, and 53.6% respectively. When drug-related adverse events were analyzed, ibuprofen resulted in significantly higher rates (34.5%) than placebo (24.9%, $p = 0.025$), but the incidence

Table 3. Comparative NSAID retail prices for a 30-day supply*

Naproxen Sodium 500 mg, BID, #60	\$27.81
Ibuprofen 800 mg, TID, #90	\$22.03
Celecoxib 200 mg, QD, #30	\$89.87

* Cost represents the average retail price from 3 local community pharmacies.

for etoricoxib (32.1%) was not different from placebo. Discontinuation rates were similar between all three groups.

Digestive system-specific drug-related adverse events were higher in the ibuprofen group (26.5%) than in the placebo group (17.6%), although no significant difference between placebo and etoricoxib (24%, 95% CI for difference = -1.1, 13.8) was shown. Out of the 221 subjects on etoricoxib, two serious clinical adverse events of the digestive system were reported. One patient experienced gastroesophageal reflux disease and one patient had a hemorrhagic gastric ulcer. A meta-analysis demonstrated the relative risk for GI-related complications with etoricoxib versus other NSAIDs was 0.44 (95% CI 0.27, 0.72; $p < 0.001$). These results suggest that etoricoxib might result in fewer gastric and duodenal ulcers compared non-selective COX inhibitors.

A summary of adverse effects reported in clinical trials is presented in Table 2.

Cost

Since etoricoxib has not been approved by the FDA, no cost information is currently available; however, similar to other selective agents, the cost of etoricoxib will be substantially more than conventional NSAIDs which are available over-the-counter. See Table 3 for comparative pricing of other NSAIDs.

Summary

Etoricoxib is a long-acting, highly selective COX-2 inhibitor, which is effective in acute gout, osteoarthritis, rheumatoid arthritis, chronic low back pain and dysmenorrhea. Its quick onset of action (less than 1 hour) helps to provide rapid pain relief. Adverse effects are similar to that observed with other COX-2 inhibitors. Given the recent events with rofecoxib and emerging evidence of a class effect, it seems prudent to select patients most likely to benefit from COX-2 selective drugs (i.e.,

those at high risk for GI bleeding) and a low risk of cardiovascular events. The role of etoricoxib as a COX-2 selective inhibitor remains to be seen and will most likely hinge on its cardiovascular safety.

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