ARTHRITIS & RHEUMATISM
Vol. 50, No. 2, February 2004, pp 598–606
DOI 10.1002/art.20007

Efficacy and Safety Profile of Treatment With Etoricoxib 120 mg Once Daily Compared With Indomethacin 50 mg Three Times Daily in Acute Gout

A Randomized Controlled Trial

Bernard R. Rubin,[1] Robert Burton,[2] Sandra Navarra,[3] Joseph Antigua,[4] John Londoño,[5] Keith G. Pryhuber,[6] Margaret Lund,[7] Erluo Chen,[8] Daryl K. Najarian,[8] Richard A. Petruschke,[8] Zafer E. Ozturk,[7] and Gregory P. Geba[8]

Objective. **To evaluate the efficacy and safety of etoricoxib and indomethacin in the treatment of patients with acute gout.**

Methods. **A randomized, double-blind, active-comparator study was conducted at 42 sites. A total of 189 men and women (≥18 years of age) who were experiencing an acute attack (≤48 hours) of clinically diagnosed gout were treated for 8 days with etoricoxib, 120 mg/day (n = 103), or indomethacin, 50 mg 3 times a day (n = 86). The primary efficacy end point was the patient's assessment of pain in the study joint (0–4-point Likert scale) over days 2–5. Safety was assessed by adverse experiences (AEs) occurring during the trial.**

Results. **Etoricoxib demonstrated clinical efficacy comparable to that of indomethacin in terms of the patient's assessment of pain in the study joint. The difference in the mean change from baseline over days 2–5 was –0.08 (95% confidence interval –0.29, 0.13) (P = 0.46), which fell within the prespecified comparability bounds of –0.5 to 0.5. Secondary end points over the 8-day study, including the onset of efficacy, reduction in signs of inflammation, and patient's and investigator's global assessments of response to therapy, confirmed the comparable efficacy of the two treatments. The etoricoxib-treated patients had a numerically lower incidence of AEs (43.7%) than did the indomethacin-treated patients (57.0%) and a significantly lower incidence of drug-related AEs (16.5% versus 37.2%; P < 0.05).**

Conclusion. **Etoricoxib at a dosage of 120 mg once daily was confirmed to be an effective treatment for acute gout. Etoricoxib was comparable in efficacy to indomethacin at a dosage of 50 mg 3 times daily, and it was generally safe and well tolerated.**

Acute gouty arthritis is the most common form of inflammatory joint disease in men over the age of 40 years (1,2). It is estimated to affect 0.5–2.8% of men, with a lower rate of occurrence among women, who experience gout primarily after menopause (3). The prevalence is much higher among individuals with a positive family history (3). Monosodium urate monohydrate crystals, which arise from abnormal metabolism of purines, cause an intense inflammatory reaction that

Supported by Merck & Company, Inc.

[1]Bernard R. Rubin, DO, MPH: University of North Texas, Fort Worth; [2]Robert Burton, MD: Quality Research for Medical Advancement, LLC, Anaheim, California; [3]Sandra Navarra, MD: University of Santo Tomas Hospital, Manila, The Philippines; [4]Joseph Antigua, MD: Chong Hua Hospital, Cebu City, The Philippines; [5]John Londoño, MD: Hospital Militar Central, Bogotá, Colombia; [6]Keith G. Pryhuber, MD: University of Rochester School of Medicine, Rochester, New York; [7]Margaret Lund, RN, Zafer E. Ozturk, MD: Merck & Company, Inc., Whitehouse Station, New Jersey; [8]Erluo Chen, MPH, Daryl K. Najarian, BS, Richard A. Petruschke, PharmD, Gregory P. Geba, MD, MPH: Merck & Company, Inc., West Point, Pennsylvania.

Dr. Rubin has served as a consultant to, and has received honoraria from, Merck, Pfizer, Wyeth, Amgen, Abbott, and Lilly; has served as a consultant to Aventis; has received honoraria from Procter and Gamble; and has received research grants from Merck, Novartis, Pfizer, Centocor, Genentech, Procter and Gamble, and TAP.

Address correspondence and reprint requests to Gregory P. Geba, MD, MPH, Merck & Company, Inc., HM-202, PO Box 4, West Point, PA 19486-0004. E-mail: gregory_geba@merck.com.

Submitted for publication July 21, 2003; accepted October 13, 2003.

results in pain, tenderness, erythema, and swelling, which manifest as acute tenosynovitis and arthritis (1–7) and typically involves the smaller appendicular joints (8,9).

While the primary symptom of acute gout is pain, optimal therapy is directed at controlling inflammation (2,4,7,10). Up-regulation of cyclooxygenase 2 (COX-2) is thought to be critical to the inflammatory process, contributing to cellular recruitment, vascular leakage, and peripheral nerve stimulation (4,10). Treatments aimed at modulating the inflammatory process have changed little over the last 30 years (11). Colchicine (an inhibitor of microtubule synthesis necessary for cell migration) and nonsteroidal antiinflammatory drugs (NSAIDs; inhibitors of both COX-1 and COX-2) are often used to treat acute attacks and have demonstrated efficacy, whereas steroid treatment has had more variable success (1,3,12–14). NSAIDs have become standard therapy (1–3,12,13), given their effects on the suppression of inflammation coupled with their analgesic properties. Indomethacin is considered the most potent NSAID for the treatment of gout, and it is typically administered at the maximum dosage of 50 mg 3 times a day (1–3,7,12).

Despite the proven efficacy of NSAIDs in acute gout, associated side effects, particularly those related to the gastrointestinal (GI) tract, are not well tolerated by many patients (15–19). The COX-2 inhibitors exhibit antiinflammatory and analgesic efficacy similar to that of nonselective NSAIDs, but with better GI tolerability (7,20–24). Etoricoxib, a highly selective COX-2 inhibitor, has shown antiinflammatory, analgesic, and antipyretic activity in models of acute and chronic pain and inflammation (25–27). In a recently reported 8-day active-comparator–controlled study of etoricoxib versus indomethacin in the treatment of acute gout, etoricoxib was shown to be comparable to indomethacin in terms of the patient's assessment of pain, as well as the patient's and investigator's global assessments of response to therapy (28). The present study was designed to replicate and confirm the efficacy of a single daily dose of 120 mg of etoricoxib in the treatment of acute gout, as compared with 50 mg of indomethacin taken 3 times a day, and to provide additional safety data in patients with acute gout.

PATIENTS AND METHODS

Study design. After meeting entry criteria and giving their informed consent, patients were randomized in equal proportions to 1 of the 2 treatment groups and were stratified according to the presence of acute monarticular versus acute polyarticular gout. The study was double-blind and double-dummy. Each patient took 1 dose of etoricoxib 120 mg or matching placebo once daily, as well as indomethacin 50 mg or matching placebo 3 times daily for a total of 8 days.

Medical history and physical examination, baseline laboratory tests (complete blood cell count [CBC], blood chemistry, urinalysis), patient's assessment of pain, and investigator's assessment of swelling, tenderness, and erythema were performed. For the majority of patients, a central laboratory performed all analyses, including serum creatinine levels, while local laboratories were used for the remainder of the patients. The patients assessed their level of pain daily, 4 hours after the first dose of the study medication. Physical examination, pill counts, and investigator's assessments were performed on days 2, 5, and 8. A final physical examination was performed 14 days after study completion. Adverse experiences (AEs) were monitored and recorded.

Selection of patients. Patients were enrolled at 42 study sites (27 in the US, and 15 in Mexico, South America, South Africa, and the Philippines). Eligible patients were men or nonpregnant women who were at least 18 years of age and were experiencing an acute attack (within 48 hours from onset) of clinically diagnosed gout, based on the American College of Rheumatology 1980 classification criteria (29), which included the presence of one of the following: urate crystals in the joint fluid, a tophus proven to contain urate crystals, or any 6 of 12 clinical, laboratory, or radiographic diagnostic criteria (29,30). A total score of 5 (of a maximum possible score of 10) on 3 symptom questions for pain (0–4-point Likert scale), tenderness (0–3-point scale), and swelling (0–3-point scale), with the pain score being at least moderate, severe, or extreme (a score of 2, 3, or 4, respectively, on the Likert scale), was required. Eligible patients also had at least 1 CBC, blood chemistry, and urinalysis performed within 1 year prior to randomization, the results of which revealed no abnormalities that would contraindicate treatment with either study medication.

Patients were excluded if they had concurrent medical/arthritic diseases that could confound the evaluation of efficacy or that contraindicated use of the study medication. Patients with a history of attacks of acute gout that had been unresponsive to NSAIDs and those who presented with acute polyarticular gout (>4 joints) were excluded because of the potential to confound the study results. Patients with a history of allergy to NSAIDs, including aspirin, ibuprofen, and indomethacin, were excluded because of potential hypersensitivity to the study medications. Low-dose aspirin ($\leq$325 mg/day) was allowed if it had been used regularly and was anticipated to be continued at a low dose during the trial. Other medications that had been used continuously for at least 2 weeks preceding the study period and were anticipated to be continued at the same dosage during the study were allowed, including allopurinol. Colchicine was allowed if it had been taken at a stable, low dose (maximum of 0.6 mg twice daily) for >30 days prior to randomization.

Efficacy and safety evaluations. At baseline and 4 hours after the daily dose of study medication (over the entire treatment period), patients assessed the level of pain in the joint identified as the primary study joint. Pain intensity in the study joint was rated by all patients on a 5-point Likert scale ranging from 0 = no pain to 4 = extreme pain. The primary

efficacy end point was the patient's assessment of study joint pain over days 2–5 of treatment.

The secondary efficacy end points over the entire treatment period (days 2–8) included the patient's assessment of pain in the primary study joint, the patient's global assessment of response to therapy, the investigator's global assessment of response to therapy, and the investigator's assessment of tenderness and swelling of the study joint, as well as the proportion of patients who discontinued treatment because of a lack of efficacy. Prespecified exploratory analyses included the proportion of patients exhibiting erythema of the study joint and the onset of efficacy in terms of the pain score at 4 hours after the initial dose of study medication. The patient's and investigator's global assessments of response to therapy (0 = excellent; 4 = poor) and the investigator's assessments of study joint tenderness (0 = no pain; 3 = patient states there is pain, winces, and then withdraws), swelling (0 = none; 3 = bulging beyond the joint margins), and erythema (present, absent, or not assessable) were conducted on days 2, 5, and 8 during clinic visits.

Safety was monitored throughout the treatment period and for 14 days after study completion. Patients were instructed to report AEs at any time during the study and were queried about AEs during office visits on days 2, 5, and 8.

Statistical analysis. The primary hypothesis was that etoricoxib 120 mg (taken once daily) would demonstrate clinical efficacy comparable to that of indomethacin 150 mg (taken in divided doses of 50 mg 3 times daily) in the treatment of acute gout, as evaluated by the mean change in the patient's assessment of pain in the study joint from baseline over days 2–5. The secondary hypothesis related to the same end point over the entire treatment period on days 2–8. Comparability was declared if the 95% confidence interval (95% CI) for the between-group difference in the patient's assessment of pain (days 2–5 [primary] and days 2–8 [secondary]) fell within the prespecified comparability bounds of ±0.5 points on the 0–4-point Likert scale. An observed mean change of >1.46 points for the patient's assessment of pain was prespecified to define a clinical response to indomethacin, based on previously published guidance (31,32), since inclusion of a placebo group was deemed unethical in this painful condition.

A sample size of 87 patients per group had 90% power to demonstrate comparability if the true (not the observed) mean difference between the etoricoxib and indomethacin groups was 0.1.

The primary and secondary efficacy end points were analyzed using a modified intent-to-treat (mITT) approach, which included all treated patients who had measurements at baseline and at least once during treatment. Missing data were imputed from the last value, which was carried forward. A per-protocol analysis was performed to support the primary approach. The mITT approach (all patients treated and randomized) was the primary and only analysis for the safety end points. No exclusions were made from the safety analyses, nor were any safety data imputed.

Individual efficacy variables were assessed by analysis of covariance, with factors for treatment group, stratum (monarticular versus polyarticular acute gout), and baseline covariate. Two-factor interactions with treatment were tested separately. The proportion of patients with erythema and the proportion of patients discontinuing treatment because of a lack of efficacy were compared between treatment groups using Fisher's exact test. The percentages of patients who experienced AEs or discontinued treatment because of AEs were summarized. Formal statistical tests for the comparison of etoricoxib with indomethacin were performed for the following prespecified safety end points: the proportion with any AE, drug-related AEs, serious AEs, and percentage discontinuing because of AEs. An additional analysis of subgroups categorized by age (≤50 years and >50 years) was performed to assess the consistency of effect for primary (pain) and secondary (patient's global assessment of response to therapy) efficacy as well as for the prespecified safety end points.

RESULTS

Disposition of patients. A total of 208 patients with acute gout were screened at 42 study centers (Figure 1). Of these, 189 patients met the study criteria and were randomized to therapy with etoricoxib 120 mg daily (n = 103) or indomethacin 50 mg 3 times daily (n = 86). Among the 19 patients who were excluded, the most common reasons for exclusion were NSAID use within 48 hours of randomization (4 patients), corticosteroid use (3 patients), history of active coronary atheroscle-

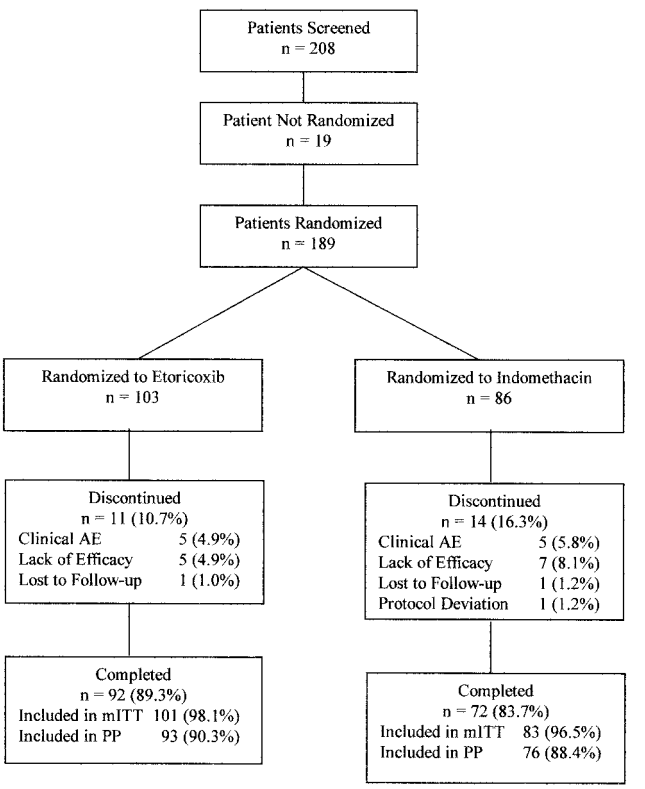

Figure 1. Disposition of the study patients. AE = adverse experience; mITT = modified intent-to-treat; PP = per protocol.

Table 1. Patient demographics and baseline characteristics

Characteristic	Etoricoxib, 120 mg (n = 103)	Indomethacin, 150 mg (n = 86)	Total (n = 189)
Sex, no. (%)			
Female	5 (5)	8 (9)	13 (7)
Male	98 (95)	78 (91)	176 (93)
Race, no. (%)			
Asian	25 (24)	23 (27)	48 (25)
Black	6 (6)	4 (5)	10 (5)
Caucasian	52 (51)	43 (50)	95 (50)
Hispanic American	15 (15)	12 (14)	27 (14)
Multiracial	5 (5)	4 (5)	9 (5)
Age, mean ± SD years	51.1 (13)	52.2 (12)	51.6 (13)
Disease classification, no. (%)			
Monarticular	81 (79)	63 (73)	144 (76)
Polyarticular	22 (21)	23 (27)	45 (24)
Primary joint affected, no. (%)			
Metatarsophalangeal (foot)	27 (26)	29 (34)	56 (30)
Ankle	26 (25)	22 (26)	48 (25)
Knee	15 (15)	10 (12)	25 (13)
Great toe proximal interphalangeal joint	10 (10)	10 (12)	20 (11)
Other	25 (24)	15 (17)	40 (21)
Lifetime total of previous attacks, no. (%)			
0	2 (2)	6 (7)	8 (4)
1–4	30 (29)	25 (29)	55 (29)
≥5	71 (69)	55 (64)	126 (67)
Attacks per year, no. (%)			
1–3 per year	56 (54)	39 (45)	95 (50)
≥4 per year	35 (34)	31 (36)	66 (35)
Not reported	12 (12)	16 (19)	28 (15)
Treatment, no. (%)			
Concomitant colchicine	12 (12)	8 (9)	20 (11)
Concomitant colchicine/allopurinol*	24 (23)	16 (19)	40 (21)

* Received at least 1 dose during the treatment period.

rotic disease with unstable angina or congestive heart failure (2 patients), active peptic ulcer disease (2 patients), and NSAID allergy (2 patients).

All 189 patients received treatment as allocated. Overall, 164 patients (87%) completed treatment. Eleven patients randomized to etoricoxib (10.7%) and 14 patients randomized to indomethacin (16.3%) discontinued treatment (Figure 1). Lack of efficacy was responsible for 4.9% of the etoricoxib and 8.1% of the indomethacin dropouts ($P = 0.385$). Mean compliance was similar for the etoricoxib (90%) and the indomethacin (89%) groups.

Demographics and disease characteristics. Treatment groups were similar with regard to demographics and disease characteristics at baseline (Table 1). Baseline values for the primary and key secondary end points are shown in Table 2.

Efficacy. *Primary end point.* The patient's assessment of joint pain over days 2–5 changed (least squares mean) by –1.79 points (95% CI –1.95, –1.63) on the 5-point Likert scale with etoricoxib treatment, a response comparable to that with indomethacin treatment, which showed a change of –1.71 points (95% CI –1.88, –1.54) (Table 2 and Figure 2). The least squares mean difference in the change from baseline (etoricoxib minus indomethacin) of –0.08 (95% CI –0.29, 0.13; $P = 0.46$), which favored etoricoxib treatment, fell within the prespecified comparability bounds of –0.5 to 0.5 points. In addition, the least squares mean change and the 95% CI for both treatments fell beyond the prespecified value that defined clinical efficacy (see Patients and Methods). These results were supported by the results of the per-protocol analysis, which also showed comparable efficacy favoring etoricoxib: –0.05 (95% CI –0.27, 0.17).

Secondary end points. The average change from baseline in the patient's assessment of pain in the primary study joint over days 2–8 was –1.99 points (95% CI –2.14, –1.84) for the group taking etoricoxib and –1.92 (95% CI –2.08, –1.76) for the group taking indomethacin, corresponding to a between-treatment difference of –0.07 (95% CI –0.27, 0.14; $P = 0.52$) (Table 2 and Figure 2), which falls within the comparability bounds of ±0.5 points. The value 4 hours after the first

Table 2. Mean change in the primary and secondary end points from baseline (modified intent-to-treat approach)*

Treatment	No. of patients	Baseline mean	Treatment mean	LS mean change (95% CI)	Difference in LS mean change (95% CI)
Primary end point (days 2–5)†					
Patient's assessment of pain (0–4 scale)					
Etoricoxib	101	2.88	1.06	−1.79 (−1.95, −1.63)	−0.08 (−0.29, 0.13)
Indomethacin	83	3.01	1.18	−1.71 (−1.88, −1.54)	
Secondary end points (days 2–8)					
Patient's assessment of pain (0–4 scale)					
Etoricoxib‡	101	2.88	0.86	−1.99 (−2.14, −1.84)	−0.07 (−0.27, 0.14)
Indomethacin§	83	3.01	0.97	−1.92 (−2.08, −1.76)	
Patient's global assessment of response to therapy (0–4 scale)					
Etoricoxib‡	101	NA	1.42	1.58 (1.37, 1.79)	−0.11 (−0.39, 0.17)
Indomethacin	86	NA	1.56	1.70 (1.48, 1.92)	
Investigator's global assessment of response to therapy (0–4 scale)					
Etoricoxib‡	101	NA	0.81	0.91 (0.74, 1.09)	−0.11 (−0.34, 0.12)
Indomethacin	86	NA	0.94	1.02 (0.84, 1.20)	
Study joint tenderness (0–3 scale)					
Etoricoxib‡	101	2.51	0.71	−1.72 (−1.84, −1.60)	−0.14 (−0.30, 0.02)
Indomethacin	86	2.58	0.89	−1.58 (−1.70, −1.46)	
Study joint swelling (0–3 scale)					
Etoricoxib‡	101	2.56	0.85	−1.65 (−1.80, −1.50)	−0.09 (−0.30, 0.11)
Indomethacin	86	2.62	0.98	−1.56 (−1.72, −1.40)	

* Negative values are indicative of improvement. LS mean = least squares mean; 95% CI = confidence interval; NA = not assessed.
† Two patients taking etoricoxib and 3 taking indomethacin were excluded from analysis because of a lack of postdose measurements over days 2–5.
‡ Two patients taking etoricoxib were excluded from analysis because of a lack of postdose measurements over days 2–5.
§ Three patients taking indomethacin were excluded from analysis because of a lack of postdose measurements over days 2–5.

dose of the study drug on day 1 also showed similar efficacy between etoricoxib –1.04 points (95% CI –1.22, –0.86) and indomethacin –0.84 (–1.02, –0.66; $P = 0.10$).

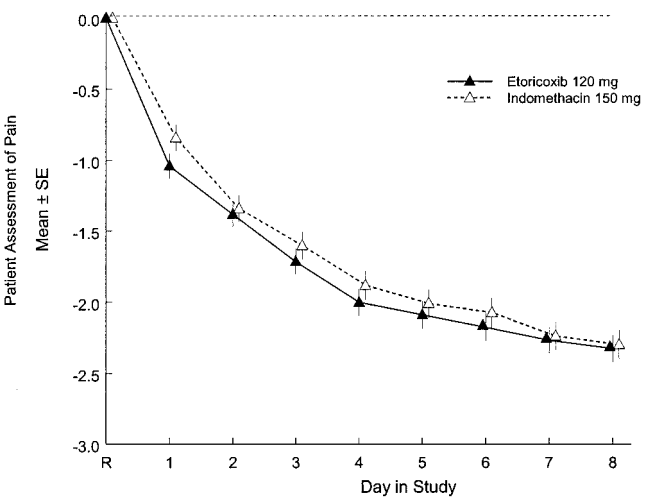

Figure 2. Patient's assessment of pain, by treatment group. Pain was assessed daily over the entire treatment period, from baseline (randomization visit [R]) to day 8, with the use of a 0–4-point Likert scale. The primary efficacy end point was the patient's assessment of pain in the study joint (0–4-point Likert scale) over days 2–5 of treatment (modified intent-to-treat approach).

Patient's assessment of pain over days 2–5 and days 2–8 was also examined in patients subgrouped by age (≤50 years and >50 years). The change from baseline over days 2–5 did not differ significantly in those taking etoricoxib (≤50 years of age –1.79 [95% CI –2.04, –1.54] and >50 years of age –1.77 [95% CI –1.99, –1.55]) compared with those taking indomethacin (≤50 years of age –1.66 [95% CI –1.93, –1.39] and >50 years of age –1.74 [95% CI –1.96, –1.52]). Treatment differences (etoricoxib minus indomethacin) within the group ≤50 years of age (–0.13 [95% CI –0.45, 0.20]) and the group >50 years of age (–0.03 [95% CI –0.33, 0.26]) fell within the comparability bounds. Similar results were found for patient's assessment of pain over days 2–8.

The patient's and investigator's global assessments of response to therapy in the total study population were also consistent with the primary end point supporting comparability. The difference in the patient's global assessment of response to therapy between etoricoxib (1.58 [95% CI 1.37, 1.79]) and indomethacin (1.70 [95% CI 1.48, 1.92]) over days 2–8 was –0.11 (95% CI –0.39, 0.17; $P = 0.43$) (Table 2). The difference in the investigator's global assessment of response to therapy between etoricoxib (0.91 [95% CI 0.74, 1.09]) and indomethacin (1.02 [95% CI 0.84, 1.20]) over days 2–8 was

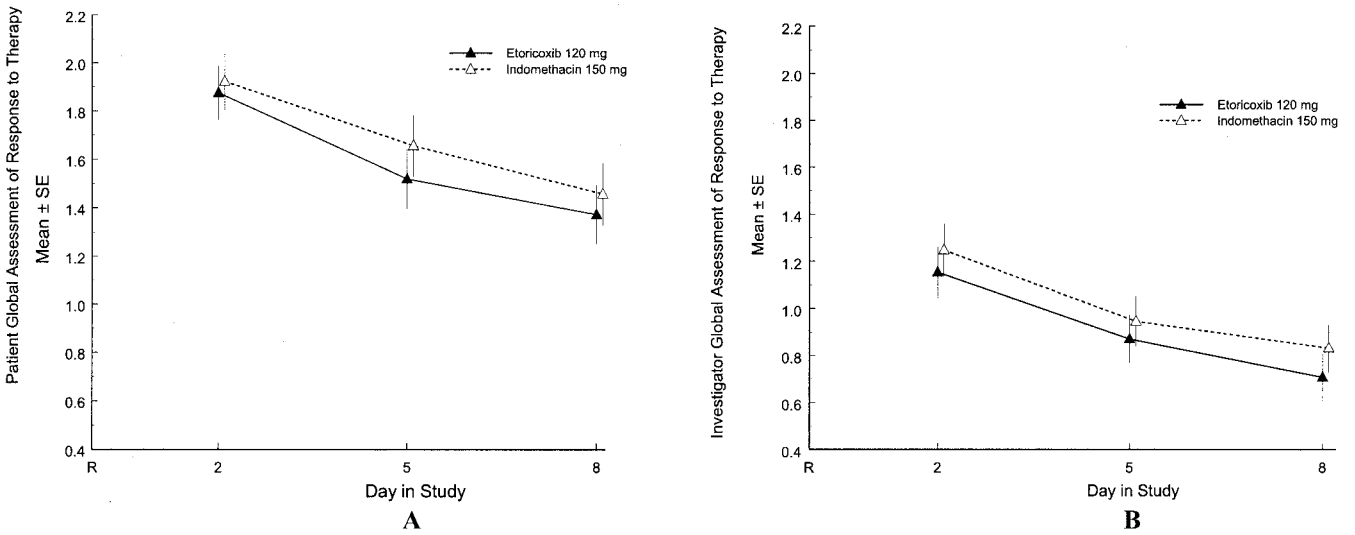

Figure 3. Patient's **(A)** and investigator's **(B)** global assessments of response to therapy, by treatment group. Global assessments were made during clinic visits on days 2, 5, and 8, with the use of a 0–4-point Likert scale. The patient's and investigator's global assessments of response to therapy were secondary efficacy end points over the entire treatment period (days 2–8) (modified intent-to-treat approach). R = randomization visit (baseline).

–0.11 (95% CI –0.34, 0.12; $P = 0.37$) (Table 2). Treatment effects for these global scores generally improved numerically over the 8-day treatment period in each group (Figure 3). The results of subgroup analysis by age for these global end points were also consistent with comparability of the two treatments in younger and older cohorts.

Differences in improvement between etoricoxib and indomethacin treatment in terms of joint tenderness (–0.14 [95% CI –0.30, 0.02; $P = 0.08$]) and joint swelling (–0.09 [95% CI –0.30, 0.11; $P = 0.36$]) were comparable (Table 2). At baseline, the proportion of patients with erythema was similar between the two treatment groups (Figure 4). Erythema was reduced to a greater extent in etoricoxib-treated patients compared with indomethacin-treated patients over days 2 and 5 ($P = 0.07$), which reached statistical significance by day 8 (7% and 18% for the etoricoxib and indomethacin groups, respectively; $P = 0.038$).

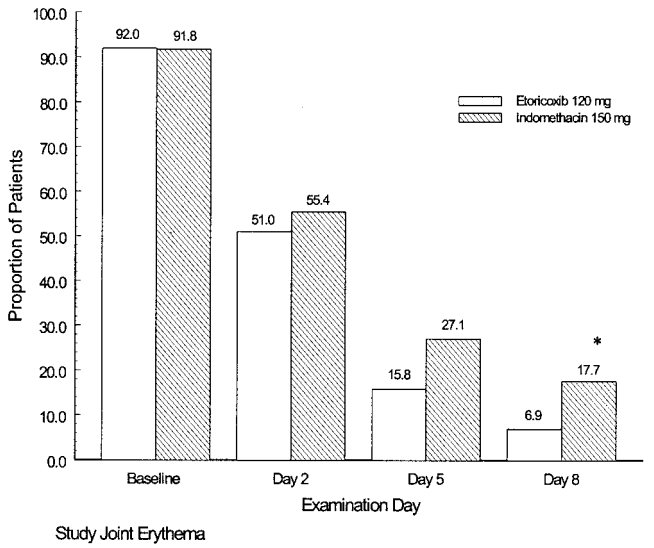

Figure 4. Proportion of patients with erythema, by treatment group. Numbers at the top of the bars are the percentages. * = $P < 0.05$ versus the etoricoxib group.

Safety. *Prespecified AEs.* One or more clinical AEs were reported by 45 patients (43.7%) taking etoricoxib and by 49 patients (57.0%) taking indomethacin ($P = 0.080$) (Table 3). The incidence of drug-related clinical AEs was 16.5% for etoricoxib and 37.2% for indomethacin ($P = 0.002$). The percentage of patients who discontinued treatment because of AEs was 4.9% for etoricoxib and 5.8% for indomethacin.

One patient in the study reported a serious clinical AE (renal failure). Prerenal azotemia preceded randomization to etoricoxib. Although this patient entered the trial with presumed dehydration (creatinine 2.0 mg/dl and blood urea nitrogen [BUN] 25.5 mg/dl), the investigator deemed this adverse experience to be probably related to the study drug. The patient recovered fully after hydration, with creatinine and BUN levels of 2.0 and 25.5 mg/dl at baseline, 3.4 and 53.5 mg/dl at peak, and 1.7 and 23.5 at recovery.

Table 3. Analysis of prespecified adverse experiences*

Clinical AE	Treatment	Proportion (%) of patients	% difference (95% CI), etoricoxib versus indomethacin	*P*
Any AE	Etoricoxib	45/103 (43.7)	−13.3 (−26.8, 1.0)	0.080
	Indomethacin	49/86 (57.0)		
Drug-related AE†	Etoricoxib	17/103 (16.5)	−20.7 (−32.8, −8.1)	0.002
	Indomethacin	32/86 (37.2)		
Serious AE	Etoricoxib	1/103 (1.0)	1.0 (−3.4, 5.3)	>0.999
	Indomethacin	0/86 (0.0)		
Discontinued due to AE	Etoricoxib	5/103 (4.9)	−1.0 (−8.6, 5.9)	>0.999
	Indomethacin	5/86 (5.8)		

* *P* values were determined by Fisher's exact test. AE = adverse experience; 95% CI = 95% confidence interval.
† Determined by the investigator to be possibly, probably, or definitely drug-related.

The mean change in serum creatinine levels on day 8 compared with baseline for both etoricoxib and indomethacin was <0.1 mg/dl, with a difference between treatments of 0.029 mg/dl (95% CI –0.02, 0.08; $P = 0.28$). Edema not considered to be drug-related occurred in 1 etoricoxib-treated patient, while drug-related fluid retention occurred in 1 indomethacin-treated patient.

Other AEs. Twice as many patients in the indomethacin group than in the etoricoxib group experienced AEs of the GI tract (20.9% versus 9.7%). Likewise, drug-related GI AEs were significantly more common in the indomethacin group (18.6%) than in the etoricoxib group (7.8%). There were no serious AEs or AEs leading to discontinuation that were related to the GI tract.

The overall incidence of cardiovascular AEs was lower with etoricoxib (6.8%) than with indomethacin (16.3%). Moreover, a lower proportion of etoricoxib-treated patients than indomethacin-treated patients experienced specific AEs, such as hypertension (4.9% versus 9.3%) and increased blood pressure (1.0% versus 4.7%).

Analysis of GI and cardiovascular AEs by age subgroup showed that differences between etoricoxib (n = 46) and indomethacin (n = 47) were similar to those in the overall population. In the older patients, GI (6.5% versus 23.4%) and cardiovascular (13.0% versus 19.1%) AEs occurred at a lower incidence in the etoricoxib group compared with the indomethacin group.

DISCUSSION

Dual COX-1– and COX-2–inhibiting NSAIDs, particularly indomethacin, are preferred agents in the treatment of acute gouty arthritis because of their ability to provide relief of pain and inflammation (1–3,12,13, 33). However, well-known side effects may temper their use (1–3,15–19,33–37). Etoricoxib, a selective inhibitor of COX-2, was designed to provide analgesic and anti-inflammatory effects with decreased GI side effects (12–26). A previous study of etoricoxib in acute gout demonstrated efficacy comparable to that of indomethacin (28). The present study, the largest study of gout reported to date, confirms and extends these results, showing that etoricoxib at a daily dose of 120 mg achieved comparable reductions in pain and inflammation and was associated with a lower incidence of adverse experiences than indomethacin at a daily dose of 150 mg.

Etoricoxib provided reductions in pain that were comparable to those observed with indomethacin. These effects appeared to be consistent in younger and older patients. Both treatments demonstrated similar onset of action, achieving reductions in the patient's assessment of pain of ~30% from baseline by 4 hours after the first dose. The rapidity of pain relief provided by etoricoxib, a drug with a 24-hour duration of action, contrasts with the commonly held misperception that once-daily medications may not provide onset that is as rapid as medications that are given in divided doses. Etoricoxib, given as a single daily dose, demonstrated an onset and durability of pain relief that, in all ways measured in this study, were equal to those of indomethacin given 3 times daily.

Improvements in the level of inflammation that is typical of gout (swelling and tenderness in the study joint) (1–7) were also comparable for both etoricoxib and indomethacin treatment. For erythema, a statistically significant improvement was observed with etoricoxib relative to that provided by indomethacin. Im-

provement in erythema, in conjunction with reductions in pain, support the theory that COX-2 is the isoform principally responsible for both the inflammation and pain that are typical of this condition. The findings are also consistent with the in vitro findings reported by Pouliot et al (10), who showed that specific inhibition of COX-2 led to a reduction in prostanoid synthesis in monosodium urate monohydrate crystal–stimulated human monocytes.

Although this was an 8-day clinical trial, the interval from day 2 to day 5 was chosen for the primary end point. This was based on guidance provided by the findings of a study by Bellamy et al (32), showing that resolution of pain is very unlikely to occur within a 4-day period without the use of effective medication. This study serves as a reference for clinical trials in acute gout because placebo-controlled trials are not considered ethical.

The population of patients involved in this trial is representative of patients who are likely to require treatment for acute gout (1,38). Most patients had monarticular gout, had had 5 or more previous attacks of gout, experienced multiple attacks each year, and had noticeable pain and inflammation at baseline. The majority of the patients in the study were men, with a mean age of 52 years. Only a small proportion of patients failed to meet the entry criteria, the most common cause being NSAID use within 48 hours of randomization. Compliance and completion rates were high for both treatment groups.

In terms of AEs, etoricoxib exhibited a lower incidence of overall AEs assessed by the investigator to be drug-related. The incidence of GI AEs was lower with etoricoxib treatment than with indomethacin. Fewer etoricoxib-treated patients than indomethacin-treated patients experienced cardiovascular AEs in this study, including increases in blood pressure or hypertension. These trends were maintained among the subgroup of patients older than 50 years, who also experienced fewer GI and cardiovascular AEs with etoricoxib than with indomethacin. Changes in serum creatinine levels were small and were similar between the 2 treatment groups. Similarities between NSAIDs and COX-2 inhibitors, including etoricoxib, in terms of their effects on renal function have previously been reported, suggesting that COX-2 inhibitors do not offer a clinically relevant advantage over nonselective inhibitors with regard to renal AEs (39,40).

In conclusion, etoricoxib treatment taken as a single 120-mg daily dose provided efficacy comparable to that of indomethacin taken as 3 50-mg daily doses in patients experiencing an acute attack of gout. Etoricoxib was generally safe and well tolerated overall in patients in this study, with a lower incidence of drug-related, GI, and cardiovascular AEs compared with indomethacin. The efficacy findings and safety advantages appeared to be retained in patients over the age of 50 years. These results support the use of etoricoxib as an alternative to indomethacin in the treatment of acute gout. Decisions regarding the choice of drug for the individual patient should be guided by risk/benefit assessments based on specific patient characteristics and evidence provided by randomized clinical trials that address the efficacy and safety of these drugs, in conjunction with cost considerations.

ACKNOWLEDGMENTS

We thank Drs. J. Boice and K. Malmstrom for help with study logistics, Drs. W. Keane and T. Dobbins for review of the manuscript and helpful comments, and Ms S. Woll for monitoring the conduct of the study.

REFERENCES

1. Harris MD, Siegel LB, Alloway JA. Gout and hyperuricemia. Am Fam Physician 1999;59:925–34.
2. Schumacher HR. Crystal-induced arthritis: an overview. Am J Med 1996;100 Suppl 2A:46S–52S.
3. Fam AG. Gout in the elderly: clinical presentation and treatment. Drugs Aging 1998;13:229–43.
4. Landis RD, Haskard DO. Pathogenesis of crystal-induced inflammation. Curr Rheumatol Rep 2001;3:36–41.
5. Reginato A, Paul H, Schumacher HR. Crystal-induced arthritis. Arch Phys Med Rehabil 1982;63:401–8.
6. Wyngaarden JB. Gout. Adv Metab Disord 1965;2:1–78.
7. Terkeltaub RA, Ginsberg MH. The inflammatory reaction to crystals. Rheum Dis Clin North Am 1988;14:353–64.
8. Van Doornum S, Ryan PF. Clinical manifestations of gout and their management. Med J Aust 2000;172:493–7.
9. Buckley TJ. Radiologic features of gout. Am Fam Physician 1996;54:1232–8.
10. Pouliot M, James MJ, McColl SR, Naccache PH, Cleland LG. Monosodium urate microcrystals induce cyclooxygenase-2 in human monocytes. Blood 1998;91:1769–76.
11. Wortmann RL. Effective management of gout: an analogy. Am J Med 1998;105:513–4.
12. Pittman JR, Bross MH. Diagnosis and management of gout. Am Fam Physician 1999;59:1799–806, 1810.
13. Emmerson BT. The management of gout. N Engl J Med 1996;334:445–51.
14. Levy M, Spino M, Read SE. Colchicine: a state-of-the-art review. Pharmacotherapy 1991;11:196–211.
15. Bjorkman DJ. Current status of nonsteroidal anti-inflammatory drug (NSAID) use in the United States: risk factors and frequency of complications. Am J Med 1999;107:3S–8S.
16. Raskin JB. Gastrointestinal effects of nonsteroidal anti-inflammatory therapy. Am J Med 1999;106:3S–12S.
17. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. N Engl J Med 1999;340:1888–99.

18. Cappell MS, Schein JR. Diagnosis and treatment of nonsteroidal anti-inflammatory drug-associated upper gastrointestinal toxicity. Gastroenterol Clin North Am 2000;29:97–124, vi.
19. McCarthy DM. Comparative toxicity of nonsteroidal anti-inflammatory drugs. Am J Med 1999;107:37S–46S.
20. Jouzeau JY, Terlain B, Abid A, Nedelec E, Netter P. Cyclooxygenase isoenzymes: how recent findings affect thinking about nonsteroidal anti-inflammatory drugs. Drugs 1997;53:563–82.
21. Donnelly MT, Hawkey CJ. COX-II inhibitors—a new generation of safer NSAIDs? Aliment Pharmacol Ther 1997;11:227–36.
22. Peura DA. Gastrointestinal safety and tolerability of nonselective nonsteroidal anti-inflammatory agents and cyclooxygenase-2-selective inhibitors. Cleve Clin J Med 2002;69 Suppl 1:SI31–9.
23. Scheiman JM. Outcomes studies of the gastrointestinal safety of cyclooxygenase-2 inhibitors. Cleve Clin J Med 2002;69 Suppl 1:SI40–6.
24. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, David B, et al, for the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000;343:1520–8.
25. Riendeau D, Percival MD, Brideau C, Charleson S, Dube D, Ethier D, et al. Etoricoxib (MK-0663): preclinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2. J Pharmacol Exp Ther 2001;296:558–66.
26. Schnitzer TJ, Hochberg MC. COX-2-selective inhibitors in the treatment of arthritis. Cleve Clin J Med 2002;69 Suppl 1:SI20–30.
27. Leung AT, Malmstrom K, Gallacher AE, Sarembock B, Poor G, Beaulieu A, et al. Efficacy and tolerability profile of etoricoxib in patients with osteoarthritis: a randomized, double-blind, placebo and active-comparator controlled 12-week efficacy trial. Curr Med Res Opin 2002;18:49–58.
28. Schumacher HR Jr, Boice JA, Daikh DI, Mukhopadhyay S, Malmstrom K, Ng J, et al. Randomised double blind trial of etoricoxib and indometacin in treatment of acute gouty arthritis. BMJ 2002;324:1488–92.
29. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yü T-F. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 1977;20:895–900.
30. Terkeltaub RA, Edwards NL, Pratt PW, Ball GV. Gout. In: Klippel JH, Weyand CM, Wortmann RL, editors. Primer on the rheumatic diseases. 11th ed. Atlanta: Arthritis Foundation; 1997. pp 230–45.
31. Altman RD, Honig S, Levin JM, Lightfoot RW. Ketoprofen versus indomethacin in patients with acute gouty arthritis: a multicenter, double-blind comparative study. J Rheumatol 1988;15:1422–6.
32. Bellamy N, Downie WW, Buchanan WW. Observations on spontaneous improvement in patients with podagra: implications for therapeutic trials of nonsteroidal anti-inflammatory drugs. Br J Clin Pharmacol 1987;24:33–6.
33. Smyth CJ. Indomethacin—its rightful place in treatment. Ann Intern Med 1970;72:430–2.
34. Karachalios GN. Treatment of acute gouty arthritis with piroxicam. Clin Exp Rheumatol 1985;3:63–5.
35. Willkens RF, Case JB, Huix FJ. The treatment of acute gout with naproxen. J Clin Pharmacol 1975;15:363–6.
36. Shrestha M, Morgan DL, Moreden JM, Singh R, Nelson M, Hayes JE. Randomized double-blind comparison of the analgesic efficacy of intramuscular ketorolac and oral indomethacin in the treatment of acute gouty arthritis. Ann Emerg Med 1995;26:682–6.
37. Maccagno A, Di Giorgio E, Romanowicz A. Effectiveness of etodolac (Lodine) compared with naproxen in patients with acute gout. Curr Med Res Opin 1991;12:423–9.
38. Currie WJ. The gout patient in general practice. Rheumatol Rehabil 1978;17:205–17.
39. Cochrane DJ, Jarvis B, Keating GM. Etoricoxib. Drugs 2002;62: 2637–51.
40. Stichtenoth DO, Frolich JC. The second generation of COX-2 inhibitors: what advantages do the newest offer? Drugs 2003;63: 33–45.

APPENDIX A: THE PROTOCOL 049 STUDY GROUP

The following investigators are members of the Protocol 049 Study Group and enrolled patients: Robert Burton, MD (Anaheim, CA), Michael Kohen, MD (South Daytona, FL), Keith G. Pryhuber, MD (Rochester, NY), Vickie G. Parrish, MD (Montgomery, AL), Ronald Rapoport, MD (Fall River, MA), Bernard R. Rubin, MD (Fort Worth, TX), Jerry L. Miller, MD (Kingsport, TN), J. Scott Toder, MD (Johnston, RI), Albert J. Razzetti, MD (Deland, FL), Shelly P. Kafka, MD (Duncansville, PA), Maria Greenwald, MD (Rancho Mirage, CA), H. Malin Prupas, MD (Reno, NV), Philip J. Molloy, MD (Plymouth, MA), Jean Higashida, MD (Martinez, CA), Jerry Green, MD (Danbury, CT), Michael A. Borofsky, MD (West Reading, PA), Charles Birbara, MD (Worcester, MA), Peter J. Winkle, MD (Cypress, CA), Craig W. Wiesenhutter, MD (Coeur d'Alene, ID), William Julius Shergy, MD (Huntsville, AL), Maren L. Mahowald, MD (Minneapolis, MN), Douglas Lain, MD (Colorado Springs, CO), Gail Kerr, MD (Washington, DC), Peter A. Holt, MD (Baltimore, MD), Philip Giordano, MD (Orlando, FL), Chester L. Fisher, MD (Newport News, VA), Walter F. Chase, MD (Austin, TX), Guillermo Tate, MD (Ciudad de Buenos Aires, Argentina), Sandra Navarra, MD (Manila, Philippines), Joseph Antigua, MD (Cebu City, Philippines), John Londoño, MD (Bogota, Colombia), Javier Basualdo, MD (Santiago, Chile), Evelyn Osio-Salido, MD (Cavite City, Philippines), Ricardo Fuller, MD (Sao Paulo, Brazil), Diego Saaibi, MD (Bucaramanga, Colombia), Louis Van Zyl, MD (Worcester, South Africa), Branca Dias Souza, MD (Sao Paulo, Brazil), Philippe Chalem, MD (Bogota, Colombia), Helmuth Reuter, MD (Tygerberg, South Africa), Janitzia Vazquez-Mellado, MD (Mexico City, Mexico), Andre Lubbe, MD (Pretoria, South Africa), and Cesar Ramos Remus, MD (Guadalajara, Mexico).