Randomised double blind trial of etoricoxib and indometacin in treatment of acute gouty arthritis

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Abstract

Objective To assess the safety and efficacy of etoricoxib, a selective cyclo-oxygenase-2 inhibitor, in comparison with indometacin in the treatment of acute gouty arthritis. Design Randomised, double blind, active comparator controlled trial. Setting 43 outpatient study centres in 11 countries. Participants 142 men and eight women (75 patients per treatment group) aged 18 years or over presenting with clinically diagnosed acute gout within 48 hours of onset. Interventions Etoricoxib 120 mg administered orally once daily versus indometacin 50 mg administered orally three times daily, both for 8 days. Main outcome measures Patients' assessment of pain in the study joint over days 2 to 5 (primary end point); investigators' and patients' global assessments of response to treatment and tenderness of the study joint (key secondary end points). Results Etoricoxib showed efficacy comparable to indometacin. Patients' assessment of pain in the study joint (0–4 point Likert scale, “no pain” to “extreme pain”) over days 2 to 5 showed a least squares mean change from baseline of −1.72 (95% confidence interval −1.90 to −1.55) for etoricoxib and −1.83 (−2.01 to −1.65) for indometacin. The difference between treatment groups met prespecified comparability criteria. All other efficacy end points, including those reflecting reduction in inflammation and analgesia, provided corroborative evidence of comparable efficacy. Significant pain relief was evident at the first measurement, 4 hours after the first dose of treatment. Prespecified safety analyses revealed that drug related adverse experiences occurred significantly less frequently with etoricoxib (22.7%) than with indometacin (46.7%) (P=0.003), although overall adverse experience rates were similar between the two treatment groups. Conclusion Etoricoxib 120 mg once daily provides rapid and effective treatment for acute gouty arthritis comparable to indometacin 50 mg three times daily. Etoricoxib was generally safe and well tolerated in this study.

Introduction

Gout is the most common form of inflammatory joint disease in men over the age of 40. Acute gout is an intense, extremely painful, inflammatory arthritis with a rapidly escalating inflammatory response resulting from formation of monosodium urate crystals in the affected joint space. Although pain is the primary symptom of acute gout, an effective treatment must target both the pain and the underlying inflammation.

The drugs most often prescribed for acute gout are the non-steroidal anti-inflammatory drugs, of which indometacin is the standard treatment. Although indometacin is widely used, its efficacy is based on few studies, and it is associated with significant side effects in the gastrointestinal tract and central nervous system. Non-selective non-steroidal anti-inflammatory drugs, including indometacin, inhibit two closely related enzymes—cyclo-oxygenase-1 and cyclo-oxygenase-2. Cyclo-oxygenase-1 is broadly and constitutively expressed, whereas cyclo-oxygenase-2 is an inducible enzyme involved in inflammatory processes. Cyclo-oxygenase-2 selective inhibitors, such as rofecoxib and celecoxib, have been shown to be as effective as non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis, rheumatoid arthritis, and acute pain. However, the efficacy of selective cyclo-oxygenase-2 inhibitors in the treatment of acute inflammatory conditions such as acute gout has not been assessed.

Unlike other inflammatory conditions, such as those caused by tissue injury or aberrant immune responses, the inflammatory stimulus for acute gout is monosodium urate crystals. Although preclinical data have shown that cyclo-oxygenase-2 protein is induced in pro-inflammatory cells exposed to monosodium urate crystals, the rapid onset of a gout attack may indicate the involvement of the early response phase of inflammation, potentially involving cyclo-oxygenase-1. Analysis of synovial fluid from patients with acute gout supports the potential role of cyclo-oxygenase-1. The efficacy of a cyclo-oxygenase-2 selective inhibitor in acute gout is therefore speculative in the absence of clinical data.

To determine whether selectively inhibiting cyclo-oxygenase-2 in a rapid and sustained manner can effectively treat the pain and inflammation of acute gouty arthritis, we compared the efficacy of etoricoxib with that of indometacin.

Methods

Study population

Eligible patients were aged 18 years or over with acute gout (onset within 48 hours) associated with moderate, severe, or extreme pain and meeting the American Rheumatology Association diagnostic criteria for acute gout (see box on bmj.com). Additional criteria included baseline evaluations showing a sum score of ≥5 for pain (0–4 point scale), tenderness (0–3 point scale), and swelling (0–3 point scale) and a complete blood count, blood chemistry, and urinalysis within one year before randomisation without clinically significant abnormalities or a normal complete blood count and serum creatinine obtained before dosing.

We excluded patients if they had acute polyarticular gout involving more than four joints; a concurrent

An additional box, table, and figure appear on bmj.com
medical or arthritic disease that could confound or interfere with the efficacy evaluation; or an unstable medical condition, including any history contraindicating the use of indomethacin, a history of cancer during the previous five years, or a history of cerebrovascular events, myocardial infarction, or coronary bypass in the previous year. We also excluded patients taking corticosteroids within one month before randomisation or taking anticoagulants, ticlopidine, clopidogrel, or digoxin. We permitted patients to continue taking aspirin (≤325 mg daily), allopurinol if taken for at least two weeks before randomisation, and colchicine (≤1.2 mg daily) if taken at a stable dose for more than 30 days before randomisation. We did not allow non-steroidal anti-inflammatory drugs within 48 hours before baseline assessments or analgesics, including aspirin, within six hours before baseline assessments and for the duration of the trial.

Study design
This was a randomised, double blind (the investigators and sponsor were blinded throughout the study), active comparator controlled study. The institutional review board or ethics review committee at each centre approved the protocol, and all patients gave written informed consent before participation. Patients were screened and, if eligible, randomised immediately (day 1), according to a computer generated allocation schedule provided by the sponsor, to receive oral administration of etoricoxib 120 mg once daily or indomethacin 50 mg three times daily. Patients took one tablet of etoricoxib or placebo from bottle A once daily in the morning and one capsule of indomethacin or placebo from bottle B three times daily (morning, afternoon, and evening). The treatment allocation was stratified for monoarticular or polyarticular acute gout. All patients completed pain assessments daily and returned to the clinic on days 2, 5, and 8 for assessment by the investigator; they also returned 14 days after the last dose for a post-study visit.

Assessment of efficacy
Efficacy end points included patients’ assessment of pain in the study joint (primary end point) and investigators’ assessments of tenderness, swelling, and erythema. We also evaluated patients’ and investigators’ global assessments of response to treatment.

The patients assessed pain in the study joint (0-4 point scale: “none,” “mild,” “moderate,” “severe,” “extreme”) at baseline, four hours after the initial dose on day 1, and approximately four hours after the first daily dose on days 2 to 8. Investigators assessed tenderness of the study joint on the basis of palpation or passive motion (0-3 point scale: “no pain” to “patient states there is pain, winces, and withdraws”), swelling (0-3 point scale: “none” to “bulging beyond joint margins”), and erythema (present or absent) at baseline and at clinic visits. Patients’ (0-4 point scale: “excellent” to “poor”) and investigators’ (0-4 point scale: “excellent” to “none”) global assessments of response to treatment were collected at clinic visits. We also assessed the proportion of patients discontinuing treatment owing to lack of efficacy.

Assessment of safety and tolerability
Investigators performed physical examinations, assessed vital signs, and took samples for laboratory tests (complete blood count, blood chemistry, and urinalysis) at baseline and at the post-study visit. They also collected samples for laboratory tests on day 8. They assessed vital signs and noted adverse experiences at all visits. Investigators evaluated all adverse experiences for intensity, seriousness, and relation to study drug while blinded to the treatment allocation.

Statistical analysis
We hypothesised that etoricoxib would show clinical efficacy comparable to indomethacin as evaluated by patients’ assessment of pain in the study joint (mean change from baseline over days 2 to 5 (primary end point) and over days 2 to 8 (secondary end point)). As prespecified in the data analysis plan, etoricoxib would be declared comparable to indomethacin if the 95% confidence interval for the between treatment difference fell within ±0.5 Likert units; these bounds were based on a consensus development (delphi) exercise in which ±0.5 was shown to be the minimum clinically important difference in osteoarthritis. The prespecified criteria for verifying the efficacy of indomethacin required that the mean change from baseline in the indomethacin group should be at least −1.46 Likert units. This criterion was based on a 95% confidence interval for 60% of the predicted treatment effect (−2.02 to −1.46), calculated using data from a study of indomethacin versus ketoprofen* and a non-treatment, observational study.

On the basis of a standard deviation of 0.71 observed in a study of postorthopaedic surgical pain with rofecoxib, n = 62 patients per group would have 95% power to show comparable efficacy if the true mean difference between etoricoxib and indomethacin was zero. We analysed continuous efficacy variables by using a covariance model including factors for treatment, stratum, and baseline response. We obtained least squares means and associated 95% confidence intervals to estimate and compare between treatment responses. We computed average responses from observed data and used the last value carried forward method for longitudinal graphs. We used Fisher’s exact test and the Wilson’s score method to compare proportions, including analysis of prespecified adverse experiences. We based analyses on an intention to treat approach (all patients with a baseline and at least one on-treatment measurement).

Results
Characteristics of the patients
Forty three study centres (hospital clinics, urgent care centres, and office practices) in 11 countries participated. A total of 31 centres enrolled 150 patients (75 in each group) between June and December 2000. Figure A on bmj.com shows a schematic representation of patient accounting throughout the study. Baseline characteristics (table A on bmj.com) and compliance rates were generally similar in both groups (around 91%).

Efficacy
Etoricoxib and indomethacin showed comparable efficacy in the treatment of acute gouty arthritis as
**Patient and investigator global assessments of response to treatment are least squares mean treatment values.** less than best possible anticipated result; 0 = none—no response, absence of drug effect; 3 = poor; 3 = = 0 = none; 1 = no pain; 1 = †0 = included in analysis for each end point (n) is based on number of patients with baseline score and at least one post = not applicable; n/N = NA.

Summary of secondary end points for days 2 to 8

<table>
<thead>
<tr>
<th>End point</th>
<th>Baseline (mean)</th>
<th>Treatment period (mean)</th>
<th>Least squares mean change from baseline (95% CI)</th>
<th>Least squares mean difference from indometacin (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenderness of study joint (0-3 scale)*†</td>
<td>Etoricoxib 120 mg (n=74/75)</td>
<td>2.51 0.72</td>
<td>-1.76 (-1.91 to -1.62)</td>
<td>-0.01 (-0.22 to 0.20)</td>
</tr>
<tr>
<td></td>
<td>Indometacin 150 mg (n=73/75)</td>
<td>2.49 0.70</td>
<td>-1.75 (-1.91 to -1.63)</td>
<td>NA</td>
</tr>
<tr>
<td>Swelling of study joint (0-3 scale)*‡</td>
<td>Etoricoxib 120 mg (n=74/75)</td>
<td>2.28 0.87</td>
<td>-1.45 (-1.61 to -1.29)</td>
<td>0.00 (-0.22 to 0.23)</td>
</tr>
<tr>
<td></td>
<td>Indometacin 150 mg (n=73/75)</td>
<td>2.52 0.97</td>
<td>-1.45 (-1.62 to -1.28)</td>
<td>NA</td>
</tr>
<tr>
<td>Patients’ global assessment of response to treatment (0-4 Likert scale)*§</td>
<td>Etoricoxib 120 mg (n=74/75)</td>
<td>NA 1.36</td>
<td>1.42 (1.20 to 1.65)</td>
<td>0.10 (-0.21 to 0.41)</td>
</tr>
<tr>
<td></td>
<td>Indometacin 150 mg (n=72/75)</td>
<td>NA 1.20</td>
<td>1.33 (1.10 to 1.56)</td>
<td>NA</td>
</tr>
<tr>
<td>Investigators’ global assessment of response to treatment (0-4 Likert scale)*‡</td>
<td>Etoricoxib 120 mg (n=74/75)</td>
<td>NA 0.83</td>
<td>0.89 (0.70 to 1.08)</td>
<td>0.01 (-0.25 to 0.28)</td>
</tr>
<tr>
<td></td>
<td>Indometacin 150 mg (n=73/75)</td>
<td>NA 0.79</td>
<td>0.88 (0.69 to 1.08)</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA = not applicable; n/N = total number of patients in analysis (n) versus total number of patients randomised to treatment group (N). (Total number of patients included in analysis for each end point (n) is based on number of patients with baseline score and at least one post-treatment score.)*

*All investigator assessments throughout the study were carried out by the same physician for a given patient.

†= none pain; 1 = patient states that there is pain; 2 = patient states that there is pain and winces; 3 = patient states that there is pain, winces, and withdraws.

‡= none = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain; 4 = extreme pain. The four hour time point indicates the assessment four hours after the initial dose of study drug on day 1, the day of the randomisation (R) visit (baseline).

§= none = no response, absence of drug effect; 3 = poor — minimal response, unacceptable; 2 = definite response, but could be better; 1 = good — good response, but less than best possible anticipated result; 0 = excellent — best possible anticipated response, considering severity of gout attack.

**Patient and investigator global assessments of response to treatment are least squares mean treatment values.**
no pain or mild pain within four hours of dosing. Of the patients who reported severe or extreme pain at baseline, 22% in the etoricoxib group and 10% in the indometacin group had mild or no pain within four hours of dosing.

Consistency of efficacy across disease types
The reduction of pain in the study joint was consistent between monarticular and polyarticular gout (P > 0.200) and across subgroups defined by concomitant use of allopurinol, colchicine, or both.

Safety
Four serious adverse experiences were reported, all in the indometacin group: vomiting and headache (determined by the investigator to be drug related), a drug overdose, and a laryngeal neoplasm (determined not to be drug related). For all four prespecified categories of adverse experiences, etoricoxib was associated with a lower incidence than indometacin (table 2). Drug related adverse experiences showed a significant difference (P=0.003); the most disparate were dizziness (4 patients in the etoricoxib group and 15 in the indometacin group), headache (1 and 5), somnolence (1 and 4), and a variety of digestive adverse experiences (6 and 17). Five patients in the etoricoxib group and six in the indometacin group had one or more laboratory finding that was considered to be an adverse experience.

Discussion
Previous work has shown that cyclo-oxygenase-2 selective inhibitors provide efficacy similar to that of non-selective non-steroidal anti-inflammatory drugs in chronic inflammatory conditions and acute pain. However, the precise roles of cyclo-oxygenase-1 and cyclo-oxygenase-2 in acute inflammatory conditions such as acute gout have not been studied. In this study, we found that etoricoxib, which rapidly and selectively inhibits cyclo-oxygenase-2, had efficacy comparable to that of indometacin, the standard treatment for acute gout. We characterised the efficacy of etoricoxib on a wide variety of clinical manifestations of gout, including measurements that assessed both pain and inflammation, and found the efficacy of etoricoxib to be comparable to that of indometacin. Etoricoxib provided pain relief comparable to indometacin as early as four hours after the initial dose, the first time point assessed. The proportion of patients reporting mild or no pain at the initial time point showed the powerful and rapid analgesic and anti-inflammatory effect of both drugs. Our results—in combination with the established pharmacology of etoricoxib—provide strong evidence in support of the hypothesis that selective inhibition of cyclo-oxygenase-2 alone is sufficient to treat the pain and inflammation of acute gout.

Few clinical trials have been performed in acute gout, and these trials enrolled small numbers of patients, so there is only suggestive evidence of the effectiveness of various treatments. This study, representing the largest controlled trial in acute gout reported to date, had a rigorous design. Patients satisfied established diagnostic criteria to ensure that they were having an attack of gout and were enrolled within 48 hours of the onset of the attack. The primary efficacy assessment was over the first four days. Given the self-limiting nature of acute gout, this design ensured that the emphasis was on the initial days of an attack, the period least likely to be influenced by spontaneous improvements that could skew the efficacy analysis. The end points chosen had been used in previous studies on acute gout but, owing to the paucity of previous studies on acute gout, are only validated in studies of osteoarthritis and analgesia.

In this study etoricoxib and indometacin were generally safe and well tolerated. Even this large study was still too small to allow for a rigorous safety assessment. The data on drug related clinical adverse experiences show that etoricoxib may be better tolerated than indometacin, but additional studies are needed to enable any definitive conclusions on safety to be drawn.

In conclusion, these results showed that etoricoxib had comparable efficacy to indometacin, proving that selective, potent, and rapid inhibition of cyclo-oxygenase-2 is sufficient to treat acute gout effectively. The demographics of the patients enrolled in this study were typical of patients with acute gout, and this, together with the diversity of the study sites, means that these results are likely to be applicable to patients with acute gout in general. The results of this study indicate that etoricoxib represents an effective treatment alternative to indometacin.

We thank Elliot Ehrich for invaluable contributions to the design of the study, Peter Merkel for helpful suggestions regarding the design study, and Ken Truitt for guidance during the course of the study. We also thank Briggs Morrison, Ned Braunstein, and Barry Gertz for their helpful comments and suggestions. The Acute Gout Study Group consisted of the

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**Table 2** Analysis of prespecified adverse experiences. Values are numbers (percentages) of patients unless stated otherwise

<table>
<thead>
<tr>
<th>Type of adverse experience</th>
<th>Etoricoxib (n=75)</th>
<th>Indometacin (n=75)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more clinical adverse experiences</td>
<td>35 (46.7)</td>
<td>49 (66.0)</td>
<td>0.141</td>
</tr>
<tr>
<td>Drug related clinical adverse experiences</td>
<td>17 (22.7)</td>
<td>25 (33.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>Serious clinical adverse experiences</td>
<td>0</td>
<td>3 (4.0)</td>
<td>0.245</td>
</tr>
<tr>
<td>Discontinued owing to clinical adverse experiences</td>
<td>2 (2.7)</td>
<td>8 (10.7)</td>
<td>0.998</td>
</tr>
</tbody>
</table>

*Fisher’s exact test.
†Determined by the investigator to be possibly, probably, or definitely drug related.
‡Drug related vomiting and headache (1 patient), non-drug related laryngeal neoplasm (1), non-drug related drug overdose (1).
I held the patient's hand and sympathetically explained that advanced diabetic retinopathy. At the end of the consultation, patient is ever "blind," at least in their hearing) because of unfortunately, she also had a severe visual handicap (no years, an amputation of one leg, and a recent cardiac infarct. I thanked for her help. The patient had had diabetes for many consulting room in a wheelchair by a caring relative, whom I

What this study adds

Etoricoxib, a cyclo-oxygenase-2 selective inhibitor, has comparable efficacy to indomethacin in the treatment of acute gouty arthritis

Etoricoxib provides rapid relief of pain and effectively treat the inflammation of acute gout; it is an effective treatment alternative to indomethacin following investigators: G Tate (Argentina); J Benit (Belgium); R Fuller, D Souza (Brazil); J Basualdo (Chile); J Londono, J Molina (Colombia); V Thous (Greece); J Orozco Alcala, J Vasquez-Mellado (Mexico); L McLean (New Zealand); J Antigua, S Navarra, E Osio-Salido (Philippines); A Lubbe, H Reuter (South Africa); W Blackburn, M Brown (AI, USA); D Arkle, D I Daik, R Kaplan, A Kavanagh, P Stein (CA, USA); G Gladstein (CT, USA); M Wooten (DE, USA); P Saxe, J Valeriano (FL, USA); C Agudelo, D Conn (GA, USA); T Schnitzer (IL, USA); D Neusdelt (KY, USA); P Holt, P Merkel (MA, USA); P Bonafele, W H Emori (OR, USA); G Gordon, H R Schumacher Jr (PA, USA); J Aelion, K Lohr (TN, USA); C Jackson (UT, USA); R Bettis (WA, USE); G Kerr (Washington DC, USA); L Warrick (WI, USA).

Contributors: HRS contributed to the design and recruitment of the study. JAB contributed to the design and clinical aspects of the study and is the guarantor. JM contributed to the recruitment of the study. All authors contributed to the writing of the paper.

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Competing interests: HRS is on the Merck arthritis advisory board and has received fees for speaking and organizing educational programmes and consultancy fees from Merck Research Laboratories and Pfizer. DFD has received fees for speaking and a consultancy fee from Merck Research Laboratories. JAR, SM, KM, and JN are employed by Merck and own shares of Merck common stock.