Celecoxib Effectively Treats Patients with Acute Shoulder Tendinitis/Bursitis

MICHELLE PETRI, STEPHEN L. HUFMAN, GREGORY WASER, HARRY CUI, MICHAEL C. SNABES, and KENNETH M. VERBURG

ABSTRACT. ***Objective.*** Shoulder tendinitis and subacromial bursitis are acute, painful inflammatory musculoskeletal conditions that may recur as a result of overuse. We investigated the efficacy of celecoxib in managing patients with acute shoulder tendinitis/bursitis.

Methods. In this double blind, placebo controlled, parallel group study, patients with acute onset shoulder tendinitis and/or subacromial bursitis were randomized to receive one of: celecoxib 400 mg followed by 200 mg bid, naproxen 500 mg bid, or placebo bid for 14 days. The primary measure of efficacy was the mean reduction in Maximum Pain Intensity at Rest, measured using a 100 mm visual analog scale, from baseline to Days 7 and 14.

Results. Of the 306 patients randomized to treatment, 254 completed the study. On Day 7, the mean reduction from baseline in Maximum Pain Intensity at Rest was significantly greater in the celecoxib group compared with the placebo group (–27.7 ± 2.75 mm vs –18.4 ± 2.63 mm, respectively; $p < 0.05$). Similarly, on Day 14, the mean reduction from baseline in Maximum Pain Intensity at Rest was greater in the celecoxib group compared with placebo (–35.0 ± 3.06 mm vs –25.0 ± 3.05 mm; $p < 0.05$). The mean reduction from baseline in Maximum Pain Intensity at Rest was also greater in the naproxen group compared with the placebo group at Day 7 (–26.4 ± 2.70 mm vs –18.4 ± 2.63 mm; $p < 0.05$), but not on Day 14. Secondary measures of efficacy also showed treatment with celecoxib to be significantly better than placebo treatment and similar to treatment with naproxen. In addition, celecoxib was well tolerated in these patients.

Conclusion. Celecoxib showed comparable efficacy to naproxen in relieving the pain of patients with acute shoulder tendinitis and/or subacromial bursitis. (J Rheumatol 2004;31:1614–20)

Key Indexing Terms:
SHOULDER TENDINITIS
SUBACROMIAL BURSITIS
COX-2-SPECIFIC INHIBITOR
CELECOXIB

Shoulder tendinitis and subacromial bursitis are major causes of acute onset of pain, and impose significant burden on the patient. The one-year prevalence estimates in diverse adult populations range from 20% to 50%[1,2]. The prevalence of this recurring condition increases with age, but its incidence in young, active people is also significant and is most frequently related to mechanical stress or repetitive injuries associated with repetitive or occupational sport activities[3,4]. In particular, shoulder disorders have been frequently associated with activities such as throwing, swimming, or gymnastics where the arm is used as a propelling force, since this can strain the extremes of the shoulder joint's range of motion[4,5].

Several nonspecific nonsteroidal antiinflammatory drugs (NSAID), including naproxen, have been shown to be effective in treating shoulder pain[3,6-13]. More aggressive therapy is used occasionally. Corticosteroid injection into the subacromial bursa is more effective than the use of nonspecific NSAID alone, but is less common and is unlikely to be performed in the primary care or emergency room setting[14]. Nonspecific NSAID are well known to be associated with both nuisance adverse events such as abdominal pain, nausea, and dyspepsia and serious upper gastrointestinal (GI) side effects including upper GI ulceration, perforation, obstruction, and bleeding[15-20].

Celecoxib is a COX-2-specific inhibitor that is effective across a wide range of painful conditions and painful mobility disorders. Its use is approved for the treatment of osteoarthritis (OA) and rheumatoid arthritis (RA)[21-25] and the management of acute pain and dysmenorrhea. In addition, the GI safety and tolerability profile of celecoxib has been shown to be superior to that of nonspecific NSAID[18,26–29]. This safety advantage is important in the

From the Department of Medicine–Rheumatology, The Johns Hopkins University, Baltimore, Maryland; Clinical Research Department, Wenatchee Valley Medical Center, Wenatchee, Washington; Clinical Studies, Comprehensive NeuroScience Inc., Melbourne, Florida; Research and Development, Pharmacia Corporation, Skokie, Illinois; and Pfizer Global Research and Development, Ann Arbor, Michigan, USA.

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M. Petri, MD, MPH, Department of Medicine–Rheumatology, The Johns Hopkins University; S.L. Hufman, MD, Clinical Research Department, Wenatchee Valley Medical Center; G. Waser, MD, Clinical Studies, Comprehensive NeuroScience Inc.; H. Cui, PhD(c); M.C. Snabes, MD, PhD, Research and Development, Pharmacia Corporation; K.M. Verburg, PhD, Pfizer Global Research and Development.

Address reprint requests to Dr. M. Petri, Department of Medicine–Rheumatology, The Johns Hopkins University, 601 North Caroline Street, Baltimore, MD 21287. E-mail: mpetri@mail.jhmi.edu

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management of acute pain conditions since nonspecific NSAID-related adverse events can occur during short-term treatment of acute conditions. For example, after one week of treatment with naproxen, 19% of patients with OA or RA had gastric ulceration detectable by endoscopy compared with 0% of individuals in the placebo or celecoxib groups ($p = 0.011$)[30].

In addition to its established use in OA and RA, there is now a growing body of data to show that celecoxib provides analgesic efficacy in a wide range of acutely painful conditions, including shoulder pain and ankle sprain[31-36]. The efficacy of celecoxib in treating acute shoulder pain has been reported in a recent multicenter, double blind, active controlled trial[31]. In this current trial, we compared the analgesic efficacy of celecoxib 200 mg bid and naproxen 500 mg bid with placebo, in the management of acute shoulder tendinitis and/or bursitis.

MATERIALS AND METHODS

Study design. This was a multicenter, randomized, double blind, placebo controlled parallel group study. Patients were assigned to receive one of the following 3 treatments for 14 days: (1) celecoxib 400 mg, followed by a dose of celecoxib 200 mg at least 8 h later on Day 1, then celecoxib 200 mg bid; (2) naproxen 500 mg bid; or (3) placebo bid.

Patients. Patients (age ≥ 18 yrs) who had experienced an acute episode of tendinitis and/or subacromial bursitis within 7 days before the first dose of study medication were eligible for inclusion. Inclusion required a patient's Maximum Pain Intensity at Rest measure of moderate to severe [i.e., at least 50 mm on a 100 mm visual analog scale (VAS)]. In addition, at least 2 of the following had to be present in the affected shoulder to be included in the study: (1) painful abduction at any degree of motion with a VAS score ≥ 50 mm; (2) painful arc of movement from 45° to 120°, again with a VAS score ≥ 50 mm; and (3) tenderness over insertion of the supraspinatus tendon or over the subacromial bursa.

Patients with the following conditions were excluded from the trial: history of uncontrolled chronic disease, surgery to the affected shoulder, history of inflammatory arthritis, significant degenerative joint disease of the shoulder, evidence of rotator cuff tear (weakness of arm elevation/not due to pain, positive "drop arm sign," or high-riding humerus) visible on shoulder radiograph, a current fracture, or chronic calcific tendinitis with a permanent range of motion loss in the affected shoulder. Patients with traumatic shoulder tendinitis (direct trauma) were not necessarily excluded, but the number of such patients was low and was evenly distributed among the treatment groups.

The protocol was reviewed and approved by an independent ethics committee prior to initiation of the study. All patients included in the trial provided written informed consent prior to participation.

Efficacy assessments

Primary endpoint. The primary efficacy endpoint was improvement in Maximum Pain Intensity at Rest from baseline to Day 7 and Day 14. Pain was measured using a 100 mm VAS, where 0 = "no pain" and 100 mm = "worst pain."

Secondary endpoints. Secondary measures of Maximum Night-time Shoulder Pain Intensity, Patient's and Physician's Global Assessment of Shoulder Tendinitis and/or Bursitis, and Range of Motion During Active Abduction were measured at baseline, Day 7, and Day 14. Modified Brief Pain Inventory-Short Form assessments were performed at baseline, Days 2–7, and Day 14. To assess efficacy using these secondary measures, the mean improvement from baseline was calculated.

Physician's Global Assessment of Shoulder Tendinitis and/or Bursitis was measured using a 5 point scale (1 = "very good — asymptomatic and no limitation of normal activities" to 5 = "very poor — very severe symptoms that are intolerable and inability to carry out all normal activities") to evaluate the overall condition of the patient's shoulder disorder. The Patient's Global Assessment of Shoulder Tendinitis and/or Bursitis utilized the 5 point scale described above to respond to the following question: "Considering all the ways the shoulder tendinitis and/or bursitis affects you, how are you doing today?"

The Range of Motion During Active Abduction was measured on a scale of 0–180°. Pain assessments using the Modified Brief Pain Inventory-Short Form were performed, whereby patients rated the pain intensity items (Worst Pain, Average Pain, Pain Over the Past 24 Hours, and Current Pain) on an 11 point scale, where 0 = "no pain" and 10 = "pain as bad as you can imagine"[37]. Patients also used the Modified Brief Pain Inventory-Short Form to rate how their pain interfered with 7 daily activities, where 0 = "does not interfere" and 10 = "completely interferes." The daily activities were: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life.

In addition, assessments of patient satisfaction were performed on Day 14. Patient's satisfaction with pain relief, ability to perform daily activities (e.g., dressing, walking, and shopping), and overall performance of study medication was assessed using a 10 point scale, where 1 = "very dissatisfied" and 10 = "very satisfied." Finally, Time to Rescue Medication was calculated as the number of days from the first dose of study medication until additional analgesia was administered.

Safety. Clinical safety was examined by monitoring the incidence of adverse events, in addition to physical examination, and examination of changes in clinical laboratory measures and vital signs from baseline to Day 14.

Statistical analysis. The sample size calculation was determined based on the improvement in Maximum Pain Intensity at Rest using a VAS[31]. Assuming that a difference of 10.5 mm (with a standard deviation of 26.4 mm) compared with placebo would be a clinically meaningful treatment difference, a sample size of 100 patients per treatment arm was calculated to have a power of at least 80%. Statistical analyses were performed on the intent-to-treat (ITT) population, which was defined as all randomized patients who received at least one dose of study medication.

For Maximum Pain Intensity at Rest, Maximum Night-time Shoulder Pain, Range of Motion During Active Abduction, Patient's and Physician's Global Assessment of Shoulder Tendinitis and/or Bursitis, and Modified Brief Pain Inventory-Short Form, the change from baseline was analyzed using ANCOVA with treatment and center as factors and the baseline value as covariate. Patients who did not require rescue medication were censored at Day 14, meaning that Day 14 was entered as their time of rescue. If a patient withdrew before Day 14, the Time to Rescue Medication was censored at the day that the patient withdrew, which was deemed to be the day of rescue medication. Log-rank tests were performed, and the proportion of patients who used rescue medication was summarized. Patient Satisfaction Assessment was analyzed by ANCOVA with treatment and center as factors and baseline Maximum Pain Intensity at Rest as covariate.

RESULTS

Patients. Of the 306 patients randomized to receive treatment, 254 completed the study (Figure 1). There were 52 patients who withdrew from the study: celecoxib, 15; naproxen, 12; and placebo, 25 (Figure 1). The most common reason for withdrawal was lack of efficacy. Demographic data, including age, sex, race, and body weight, were similar across all groups (Table 1). At baseline, scores for Maximum Pain Intensity at Rest were similar in all treatment groups. Other pain assessment scores and the baseline measurement of Range of Motion During Active Abduction

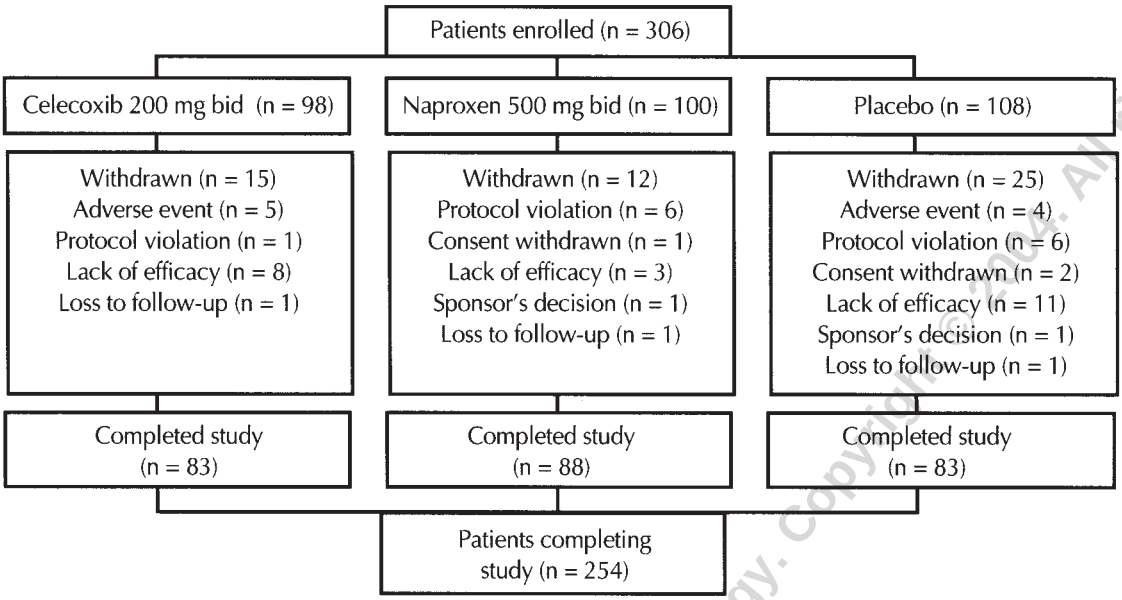

Figure 1. Patient disposition.

Table 1. Baseline demographic and clinical characteristics of study patients at baseline. Data are mean ± SEM unless otherwise indicated.

	Celecoxib 200 mg bid, n = 98	Naproxen 500 mg bid, n = 100	Placebo, n = 108	p
Age, yrs				
Mean	47.9	48.0	50.5	NS
Range	18–83	20–78	18–83	
Sex, male, n (%)	63 (64)	62 (62)	72 (67)	NS
Body weight, kg				
Mean	87.0	87.7	85.1	NS
Range	43.3–135.9	49.0–154.5	49.9–143.6	
Race, n (%)				
White	89 (91)	88 (88)	98 (91)	NS
Black	7 (7)	5 (5)	4 (4)	
Asian	1 (1)	2 (2)	1 (1)	
Not listed	1 (1)	2 (5)	5 (5)	
Maximum Pain Intensity at Rest, mm	70.4 ± 1.32	69.9 ± 1.50	69.3 ± 1.33	NS
Maximum Night-time Shoulder Pain intensity, mm	74.8 ± 1.61	69.8 ± 1.86	68.6 ± 1.99	NS
Patient's Global Assessment of Shoulder Tendinitis and/or Bursitis	3.3 ± 0.06	3.2 ± 0.06	3.2 ± 0.05	NS
Modified Brief Pain Inventory-Short Form–Worst Pain	8.0 ± 0.12	7.4 ± 0.16	7.8 ± 0.13	0.013*
Modified Brief Pain Inventory-Short Form–Interference with Function	4.8 ± 0.18	4.6 ± 0.19	4.6 ± 0.17	NS
Range of Motion During Active Abduction (°)	93.7 ± 3.06	97.4 ± 3.08	97.9 ± 3.23	NS

NS: not significant.

were not different in the 3 groups at baseline. The one exception was the Modified Brief Pain Inventory-Short Form category of Worst Pain, for which scores were significantly lower in the naproxen group compared with the celecoxib or placebo groups (p = 0.013) (Table 1).

Efficacy assessments

Primary endpoints. At Day 7, the mean reduction in Maximum Pain Intensity at Rest was significantly greater in the celecoxib group compared with the placebo group (–27.7 ± 2.75 mm vs –18.4 ± 2.63 mm, respectively; p <

0.05) (Figure 2). Similarly, at Day 14, the mean reduction in Maximum Pain Intensity at Rest was significantly greater in the celecoxib group compared with placebo (–35.0 ± 3.06 mm vs –25.0 ± 3.05 mm; $p < 0.05$). Similar reductions were observed in the naproxen treatment group compared with the placebo group at Day 7 (–26.4 ± 2.70 mm vs –18.4 ± 2.63 mm; $p < 0.05$). In contrast to the celecoxib group, however, a statistically significant difference was not observed at Day 14.

Secondary endpoints. Physician's Global Assessment of Shoulder Tendinitis and/or Bursitis was significantly improved in the celecoxib group compared with placebo, at both Day 7 and Day 14 ($p < 0.05$) (Table 2). In contrast, these same measures were not significantly improved over placebo in patients treated with naproxen. The mean changes in Maximum Night-time Shoulder Pain were significantly greater in both the celecoxib and naproxen groups compared with the placebo group at Day 7, but not at Day 14. Similarly, mean changes in the Patient's Global Assessment of Shoulder Tendinitis and/or Bursitis scores in the celecoxib and naproxen groups were significantly superior to those in the placebo group at Day 7 but not at Day 14. Mean change from baseline in Range of Motion During Active Abduction was statistically greater in the naproxen group compared with placebo at Day 14 only (29.49 ± 3.41 mm and 19.75 ± 2.85 mm, respectively; $p < 0.05$). At Day 14, celecoxib was also associated with an improvement in Range of Motion During Active Abduction (27.29 ± 2.88), although the difference versus placebo was not statistically significant.

Patient Satisfaction with Pain Relief scores performed at the end of the study (Day 14) were significantly improved in patients who had received celecoxib and naproxen compared with those who had received placebo (6.0 ± 0.35 mm, 6.1 ± 0.33 mm vs 4.9 ± 0.35 mm, respectively; $p < 0.05$). Patient Satisfaction with Daily Activity at Day 14 was also improved in the naproxen group compared with placebo (6.2 ± 0.32 mm vs 5.1 ± 0.35 mm, respectively; $p < 0.05$). In the celecoxib group, the mean Patient Satisfaction with Daily Activity at Day 14 was 6.0 ± 0.35, which, although higher than that for placebo, was not statistically different.

The majority of patients participating in this study completed the 14 day period without taking rescue medication. No statistical differences were observed between treatment groups in Time to Rescue Medication, and the proportion of patients requiring rescue medication was similar across all 3 groups (Table 2).

Figure 3 shows the results of the Modified Brief Pain Inventory-Short Form performed on Days 2–7 of the study. Patients who had received either celecoxib or naproxen experienced a greater reduction in the Modified Brief Pain Inventory-Short Form assessment of Worst Pain, compared with those who had received placebo at Days 4–7 (Figure 3A). Patients in both active treatment groups demonstrated a greater reduction in the Modified Brief Pain Inventory-Short Form assessment of Pain Interference with Function (composite score) than patients in the placebo group (Figure 3B). The difference compared to placebo was apparent a day earlier in the celecoxib group (at Day 3) than in the naproxen group (Figure 3B). This pattern of improvement was mirrored in the Modified Brief Pain Inventory-Short Form assessments of Current Pain and Average Pain. In both these assessments, the mean reduction in pain intensity from baseline in the celecoxib group was significantly greater compared with placebo at Days 3–7 whereas the mean reduction in pain intensity in the naproxen group was significantly greater compared with placebo at Days 4–7 (data not shown). No significant differences were observed between treatment groups in terms of Pain Over the Past 24 Hours (data not shown).

Safety. The incidences of adverse events occurring in the celecoxib, naproxen, and placebo groups were 36.7%, 36.0%, and 29.6%, respectively. The most common adverse

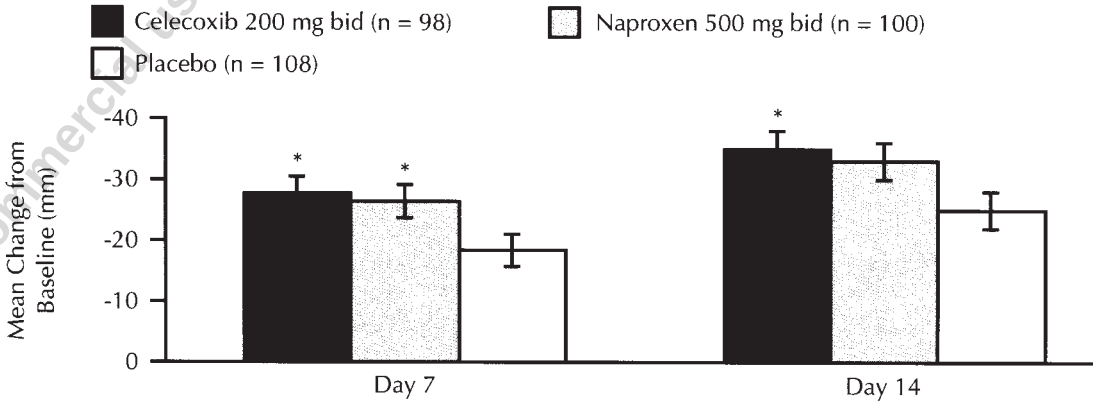

Figure 2. Mean change from baseline in Maximum Pain Intensity at Rest measured on 100 mm VAS, where 0 = "best score" and 100 = "worst score." *$p < 0.05$ compared to placebo.

Table 2. Physician's Global Assessment of Shoulder Tendinitis/Bursitis, Maximum Night-time Shoulder Pain Intensity, Patient's Global Assessment of Shoulder Tendinitis and/or Bursitis, and Range of Motion During Active Abduction, Patient's Satisfaction at End of Study, and Proportion of Patients Requiring Rescue Medication. All data are mean ± SEM unless otherwise indicated.

	Celecoxib 200 mg bid, n = 98	Naproxen 500 mg bid, n = 100	Placebo, n = 108
Mean change from baseline in Physician's Global Assessment of Shoulder Tendinitis/Bursitis (mm) at			
Day 7	–0.98 ± 0.09*	–0.89 ± 0.10	–0.66 ± 0.08
Day 14	–1.18 ± 0.11*	–1.17 ± 0.12	–0.87 ± 0.10
Mean change from baseline in Maximum Night-time Shoulder Pain Intensity (mm) at			
Day 7	–30.7 ± 2.60*	–27.7 ± 2.93*	–18.1 ± 2.83
Day 14	–38.6 ± 3.08	–33.2 ± 3.19	–27.5 ± 3.30
Mean change from baseline in Patient's Global Assessment of Shoulder Tendinitis and/or Bursitis at			
Day 7	–0.81 ± 0.09*	–0.74 ± 0.10*	–0.48 ± 0.07
Day 14	–1.02 ± 0.11	–0.90 ± 0.10	–0.76 ± 0.10
Mean change from baseline in Range of Motion During Active Abduction (°) at			
Day 7	17.74 ± 2.14	18.23 ± 3.35	15.78 ± 2.44
Day 14	27.29 ± 2.88	29.49 ± 3.41*	19.75 ± 2.85
Patient satisfaction at end of study			
Satisfaction with Pain Relief	6.0 ± 0.35*	6.1 ± 0.33*	4.9 ± 0.35
Satisfaction with Daily Activity	6.0 ± 0.35	6.2 ± 0.32*	5.1 ± 0.35
Satisfaction Overall	6.1 ± 0.35	6.0 ± 0.33	5.0 ± 0.34
Rescue medication (at least 1 tablet)			
Yes, n (%)	6 (6)	4 (4)	8 (7)
Median time, days	> 14	> 14	> 14

* $p < 0.05$ vs placebo.

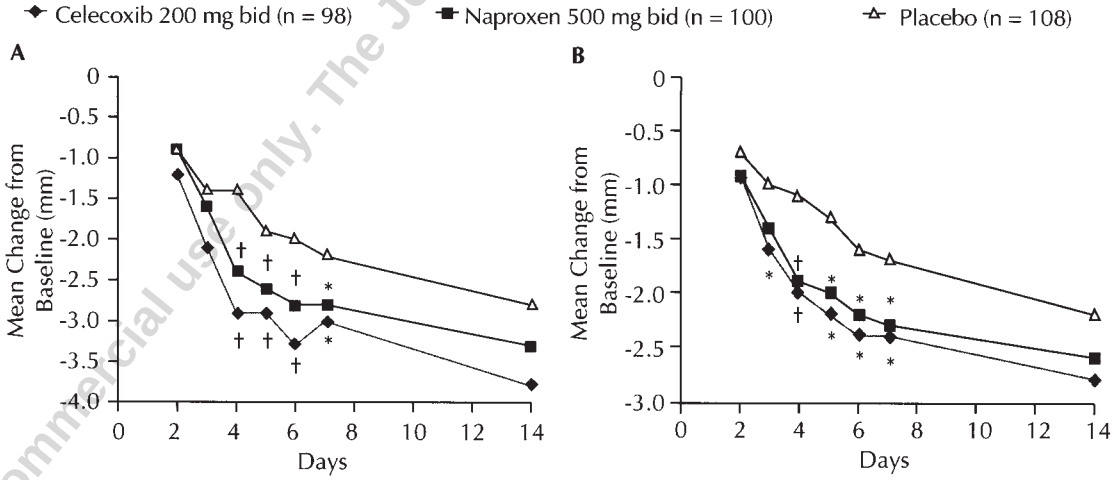

Figure 3. Mean change from baseline in Modified Brief Pain Inventory-Short Form scores of (A) Worst Pain and (B) Interference with Function. Pain scores were measured on a 10 point scale where 0 = "no pain" and 10 = "pain as bad as you can imagine." *$p < 0.05$ vs placebo; †$p < 0.01$ vs placebo.

events were headache, dyspepsia, and nausea. The incidence of headache was similar among the 3 treatments groups (7.1%, 9.0%, and 10.2% for celecoxib, naproxen, and placebo, respectively). Naproxen was associated with a numerically higher incidence of dyspepsia (7.0%) compared with the celecoxib (4.1%) and placebo groups (0.0%). The incidence of nausea was similarly higher in patients who received naproxen (6.0%) compared with those who

received celecoxib (3.1%) or placebo (1.9%). The number of withdrawals due to any adverse event in the celecoxib group was similar to that in the placebo group (5 vs 4 patients, respectively). No clinically meaningful changes were noted in the clinical laboratory or vital sign data.

DISCUSSION

The efficacy of celecoxib in the treatment of acute shoulder tendinitis and/or subacromial bursitis was demonstrated in this study by the observed mean change in Maximum Pain Intensity at Rest at both Day 7 and Day 14. The efficacy of celecoxib in this acute, often recurrent, inflammatory pain condition was supported further by the results from the secondary efficacy measures. Of particular note, the endpoints of Maximum Night-time Shoulder Pain and Patient's Global Assessment of Shoulder Tendinitis and/or Bursitis showed a statistical difference between both active treatment groups versus placebo at Day 7. In addition, functional improvement was observed in the celecoxib treatment group compared with the placebo group in mean change from baseline for the Modified Brief Pain Inventory-Short Form Composite Pain Interference score as early as Day 3, which was a day earlier than observed in the naproxen group. However, no treatment difference could be detected in these endpoints by Day 14. Given that the tendinitis/bursitis tends to be a self-limiting condition and that patients were allowed to enter the study up to 7 days after the onset of shoulder pain, by Day 14, the patients were already up to 21 days after the onset of pain, when the natural history of the condition may lead to an overall resolution of their acute pain. The self-limiting nature of this acute pain condition is supported by the continued improvement after Day 7 of patients receiving placebo. Indeed, the response at Day 14 in the placebo group in this study was greater than that observed in the previous study of shoulder pain[14]. Since maximal daily pain may be decreased by Day 14, the sensitivity to detect a significant treatment difference may be limited. Thus, the Day 7 endpoint may be more appropriate for measurement of efficacy and for assessing the clinical message.

The finding that celecoxib was as efficacious as naproxen in this current placebo controlled trial supports the earlier work by Bertin, *et al*, which found that celecoxib 200 mg bid is as effective as naproxen 500 mg bid in the management of acute shoulder pain[31]. Our data also add to the growing body of evidence that, in addition to its established use as an analgesic and antiinflammatory agent in OA and RA, celecoxib is efficacious in the management of pain in a broad range of conditions, including postorthopedic surgical pain[32] and acute soft-tissue injury[34-36].

In this current study, celecoxib 200 mg bid provided analgesic efficacy in patients with acute shoulder tendinitis and/or bursitis without compromising tolerability.

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