Efficacy and tolerability of celecoxib compared with diclofenac slow release in the treatment of acute ankle sprain in an Asian population

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ABSTRACT

Introduction: Cyclooxygenase (COX)-2 selective inhibitors are attractive candidates for treatment of ankle sprain because of their efficacy as anti-inflammatory and analgesic agents and their overall safety, including lack of effect on platelet aggregation. The objective of this study was to assess the efficacy and tolerability of celecoxib compared with diclofenac slow release (SR) in the treatment of acute ankle sprain in an Asian population.

Methods: In this seven-day, multicentre, double-blind, randomised, parallel-group trial, 370 patients with first- or second-degree ankle sprain occurring at or less than 48 hours prior to the first dose of study medication were randomised to receive celecoxib 200 mg bid (189 patients) after a 400 mg loading dose or diclofenac SR 75 mg bid (181 patients). Patients were required to demonstrate moderate to severe ankle pain on weight bearing (45 mm or greater on a 100 mm visual analogue scale [VAS]) at baseline. The primary efficacy end point was the patient's assessment of ankle pain (VAS on full weight bearing) on day 4.

Results: Celecoxib was as effective as diclofenac SR in improving the signs and symptoms of ankle sprain. At day 4, mean VAS scores for celecoxib and diclofenac SR had decreased to 28 mm and 30 mm, respectively. Treatment differences were not statistically significant. Incidence of upper gastrointestinal adverse events was low in both treatment groups (0.5 percent versus 2.2 percent for celecoxib and diclofenac SR, respectively).

Conclusion: Celecoxib, a COX-2 selective inhibitor, is as effective as diclofenac SR in treating ankle sprains. With its platelet-sparing properties, celecoxib may offer an advantage over diclofenac SR in managing musculoskeletal injuries.

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INTRODUCTION

Ankle sprains are among the most common soft-tissue injuries, occurring at a rate of approximately 23,000 per day in the United States, in both athletes and non-athletes[1]. Approximately 85% of all ankle injuries are inversion sprains of the lateral ligaments[2,3]. The anterior talofibular ligament is the most susceptible to injury; although sprains can also occur with the calcaneofibular ligament[3].

The main goals of therapy are pain relief, reduction of inflammation, and restoration of normal function. Conventional treatment for ankle sprains includes the RICE protocol (rest, ice, compression, elevation) as well as protected weight bearing, early mobilisation, and isometrics. The American Academy of Orthopaedic Surgeons recommends the use of these non-pharmacological therapies plus non-cyclooxygenase-2 (COX-2) selective nonsteroidal anti-inflammatory drugs (NSAIDs) for the initial treatment of ankle sprain[4].

Clinical trials have demonstrated that non-COX-2 selective NSAIDs can ameliorate the symptoms of ankle injury and other acute musculoskeletal injuries, reduce inflammation, and aid in the return to full function. Non-COX-2 selective NSAIDs such as diclofenac[5,6], piroxicam[7-9], nimesulide[10,11], naproxen[8,11], and ibuprofen[12,13] are all commonly used as adjuvant therapy in the treatment of acute ankle injuries.

NSAIDs reduce pain and inflammation by inhibiting COX[14], which exists as 2 isoforms. COX-1 is a constitutive form present in many tissues and is necessary for physiological (homeostatic) functions, including gastric mucosal protection and normal platelet aggregation. COX-2 is an inducible form expressed locally in inflamed tissues[15,16]. Non-COX-2 selective NSAIDs inhibit both COX-1 and COX-2[17,18].

While non-COX-2 selective NSAIDs have established efficacy in treating pain and inflammation and expediting return to normal function, they have also been associated with upper gastrointestinal (UGI) mucosal injury (e.g. ulceration, perforation, and haemorrhage) and increased risk of bleeding due to a reduction in platelet aggregation[19-21]. The effects of non-COX-2 selective NSAIDs on platelet function may be of particular concern in acute musculoskeletal injuries where bleeding secondary to trauma is common.

COX-2 selective inhibitors provide analgesic and anti-inflammatory efficacy with less of the toxicity that is associated with COX-1 inhibition[22,23]. Celecoxib does not have any clinically significant anti-platelet effects. Furthermore, it is well tolerated with a favourable UGI profile, including less ulceration and fewer serious adverse events compared with non-COX-2 selective NSAIDs[24-27].

We undertook this study to evaluate the efficacy of celecoxib compared with diclofenac slow release (SR) in the treatment of acute first- or second-degree ankle sprain and to assess the UGI tolerability of these drugs in an Asian population.

METHODS

Adult patients (aged ≥18 years) who sustained a first- or second-degree ankle sprain in the lateral aspect (specifically the anterior talofibular ligament and/or the calcaneofibular ligament) no more than 48 hours prior to the first dose of study medication, and who presented with moderate to severe pain according to the patient's assessment of ankle pain visual analogue scale ([VAS] ≥45 mm) on full weight bearing were eligible for participation in the study. Patients were required to have a minimum rating of 2 for the patient's global assessment of ankle injury and patient's assessment of normal function/activity at the time of screening. In the investigator's opinion, patients had to be eligible for therapy with an anti-inflammatory agent and/or analgesics to control their symptoms. All women of childbearing age had to be using adequate contraception and were required to have a negative urine pregnancy test.

Patients were excluded if they had a similar injury of the same joint within six months prior to the start of the study; oesophageal, gastric, or duodenal ulcer; active gastrointestinal (GI) disease; a history of clinically significant renal or hepatic disease; or osteoarthritis or rheumatic disease, including rheumatoid arthritis. They were also excluded if they had received treatment with an intra-articular injection of a corticosteroid or hyaluronic acid in any joint within eight weeks of the first dose of study medication, or if they had received any oral or intramuscular corticosteroid within 30 days of the first dose of study medication. Additional criteria for exclusion were use of an analgesic within six hours, or use of non-COX-2 selective NSAIDs, COX-2 selective inhibitors, or other medications that could potentially confound the assessment of analgesia (e.g. muscle relaxants, neuroleptics, tricyclic antidepressants, sedative hypnotics, and anxiolytics) within 24 hours of the first dose of study drugs.

This double-blind, double-dummy, randomised, active-comparator, parallel-group study was conducted at 26 centres in eight geographical areas in Asia (China, Hong Kong, Indonesia, Malaysia, Philippines, Singapore, Taiwan, and Thailand) between September 6, 2001 and July 11, 2002. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and with local laws and regulations relevant to the use of new therapeutic agents in each country. All study participants were informed of the nature and potential risks of the study prior to any study-related procedure and written informed consent was obtained from participants.

Patient eligibility was determined at a screening visit through medical history and physical examination compatible with a diagnosis of ankle sprain. Prior to treatment, assessments of pain, injury, and function were performed, as well as pregnancy tests for female patients. The physician's global assessment of ankle injury was used to grade injury severity on a 5-point scale ranging from 1 (very mild signs and symptoms of ankle sprain) to 5 (very severe signs and symptoms).

The required moderate to severe pain criteria were met if the patient reported a score of 45 mm or more on the patient's assessment of ankle pain VAS on weight bearing, a 100 mm scale ranging from 0 (no pain) to 100 (most severe pain). On the patient's global assessment of ankle injury, patients were asked, "Considering all the ways your ankle injury affects you, how are you doing today?" Responses were recorded on a 5-point scale ranging from 1 (no symptoms and no limitation of normal activities) to 5 (very severe, intolerable symptoms, and inability to carry out all normal activities).

For the patient's assessment of normal function/activity, patients were asked, "How does your ankle injury affect your walking and normal activity?" Patients responded on a 5-point scale ranging from 1 (normal walking/activity without pain) to 5 (severely restricted walking due to pain, and inability to resume normal activities).

Follow-up visits included a visit on day 4 and the final visit (day 8±1). On all follow-up visits, the patient's assessment of ankle pain VAS and patient's and physician's global assessments of ankle injury were recorded. Adverse events were also recorded on day 4 and the final visit. At the final visit, the patient's and physician's satisfaction assessments were recorded by asking the question: "How willing are you to use the same medication again for an ankle injury?" Responses were based on a 10-point scale ranging from 1 (very unwilling) to 10 (very willing).

If all eligibility criteria were satisfied, patients were randomised to celecoxib or diclofenac SR according to the order in which they were enrolled in the study. A computer-generated randomisation schedule prepared by the sponsor prior to the start of the study was used to assign subjects to a treatment regimen. Separate randomisation schedules were prepared for patients with a baseline assessment of ankle pain VAS of ≤60 mm and VAS of ≥61 mm. 25 patients with a medial ankle sprain injury (eversion or outward movement) were inadvertently enrolled in the study and randomised to treatment. These subjects are included in the results presented here, but an additional subset analysis excluding this population was also conducted.

To achieve the double dummy effect, each patient took two capsules and one tablet as a loading dose on the first day, then one capsule and one tablet (one active treatment and one placebo treatment) bid for the duration of the study. Randomised patients received either celecoxib or diclofenac SR twice daily with matching placebo for seven days as follows: patients randomised to celecoxib took two 200 mg capsules and one placebo tablet as a loading dose, and one 200 mg capsule and one placebo tablet twice daily for the duration of the study. Patients randomised to diclofenac SR took two placebo capsules and one 75 mg diclofenac tablet as a loading dose, and one placebo capsule and one 75 mg diclofenac tablet twice daily, for the duration of the study. Patients were instructed to take their medication with meals in the morning and evening.

Celecoxib 200 mg bid was chosen as a representative analgesic dose for treatment of pain associated with acute first or second-degree ankle sprain. Diclofenac SR 75 mg bid was selected based on proven efficacy (relative to placebo) for the management of acute pain.

Both the investigator and patient were blinded to the study. Unblinding was restricted to emergency situations and was done only if knowledge of the study medication was necessary to properly treat the patient. When the treatment blind was broken, the reason and the date were recorded and signed by the investigator.

During the treatment period, no other analgesic medications were permitted, e.g. non-COX-2 selective NSAIDs, paracetamol, opioids, and tramadol. However, low-dose aspirin (≤325 mg/d) for cardiovascular prophylaxis was permitted. Other medications not allowed during the trial were diuretics, anticoagulants, lithium, digoxin, and anti-ulcer drugs. The use of non-pharmacological therapies, including traditional RICE, were permitted if considered the standard of care by the investigator.

The primary measure of efficacy was the day 4 patient's assessment of ankle pain VAS on full weight bearing, during which both feet are on the floor and full body weight is placed on the affected leg while standing and walking. Secondary measures included the patient's assessment of ankle pain VAS at final visit, the proportions of subjects improving by at least 20 mm on the VAS scale on day 4 and the final visit, and the weighted average score from days 1 through 8; patient's global assessment of ankle injury on day 4 and the final visit, the proportions of subjects improving by one or more grades on day 4 and the final visit, and the weighted average assessment from days 1 through 8; the patient's assessment of normal function/activity on day 4 and final visit; the physician's global assessment of ankle injury on day 4 and final visit and the weighted average score from days 1 through 8; and the patient's and physician's satisfaction assessments.

Patient's assessment of ankle pain (VAS), patient's global assessment of ankle injury, and patient's assessment of normal function/activity are well-established measurements for analgesic activity. The patient's and physician's satisfaction assessments have provided information consistent with more objective assessments of analgesic efficacy in previous acute ankle sprain studies and were expected to provide analogous information in this study[28,29].

Safety was assessed by the incidence and type of adverse events, and any clinically significant changes from baseline to final visit in physical examination findings. In addition to individual adverse events, composite UGI tolerability was evaluated. A UGI event was defined as at least one event of moderate to severe nausea, abdominal pain, or dyspepsia.

The sample size of 168 subjects per active treatment arm was based upon the day 4 VAS score; the maximum clinically-acceptable difference for declaring non-inferiority, corresponding to the upper

bound of the 95% confidence interval (CI), where the difference between the two treatment groups was 7 mm, based upon a 0 to 100 mm VAS. Assuming a standard deviation of 23 mm and a Type I error rate of 0.050, this study had 80% power. Assuming a differential of 5% between the intent-to treat (ITT) and the per protocol analysis (PPA) population, a total of 370 subjects were to be randomised.

Patients were included in the modified ITT (mITT) population if they were randomised, received at least one dose of study medication, and had at least one follow-up efficacy measure that included the VAS pain score. The PPA population included all patients who had no major protocol violations, at least one post-baseline VAS assessment, had cumulative 80% to 120% drug compliance at day 4 and took a full-loading dose (two capsules and one tablet) on day 1, and had completed the day 4 assessment. Consistent with the International Conference on Harmonisation (ICH) guidelines for testing non-inferiority, efficacy analyses were carried out on an evaluable or PPA population.

For statistical analyses, the computer programme, SAS (SAS Institute Inc, Cary, NC, USA) was used. For baseline characteristics, continuous measures such as age and baseline VAS scores were analysed using a general linear model with effects for treatment and centre. Gender and race were analysed using two-tailed Fisher's exact tests. Ordered categorical data such as global assessments were analysed using the Cochran-Mantel-Haenszel (CMH) test controlling for investigational site.

An analysis of covariance (ANCOVA) model with centre and treatment as fixed effects and pre-treatment/baseline VAS as a covariate was used to analyse the primary efficacy measure (patient's assessment of ankle pain VAS on day 4).

For secondary efficacy analyses, weighted averages from days 1 through 8 were calculated as the area under the curve using the trapezium rule, including imputed values when necessary, and were divided by seven days. Continuous measures were analysed using ANCOVA with centre and treatment as fixed effects and pre-treatment/baseline as a covariate. All ordered categorical responses were analysed using the CMH test controlling for investigational site.

Kaplan-Meier product-limit estimates were produced for the number of days to return to normal function/activity, with normal function defined as grade 1 on the patient's assessment of normal function/activity, or improvement in function of ≥2 grades. Responder analyses were conducted using a logistical regression model that included treatment group and baseline severity. Imputed values were included when necessary.

When data were missing from the mITT efficacy analyses, the last observation carried forward method was used. Any missing post-treatment observations were extrapolated. No imputation was applied to the PPA or safety populations, or for day 4 VAS on weight-bearing data.

All patients who took at least one dose of study medication were included in the safety population used for all adverse event and tolerability analyses. The incidence of UGI events was analysed using a two-tailed Fisher's exact test for comparing between types of treatment.

RESULTS

Of the 370 patients who were randomised to treatment (celecoxib, 189; diclofenac SR, 181), 20 patients withdrew (seven in the celecoxib group and 13 in the diclofenac SR group, Fig. 1). Reasons for withdrawal included loss to follow-up, pre-existing violation of protocol criteria, protocol non-compliance, and adverse events. 346 patients were included in the PPA cohort, and 366 patients were included in the mITT cohort. All 370 patients were included in safety analyses.

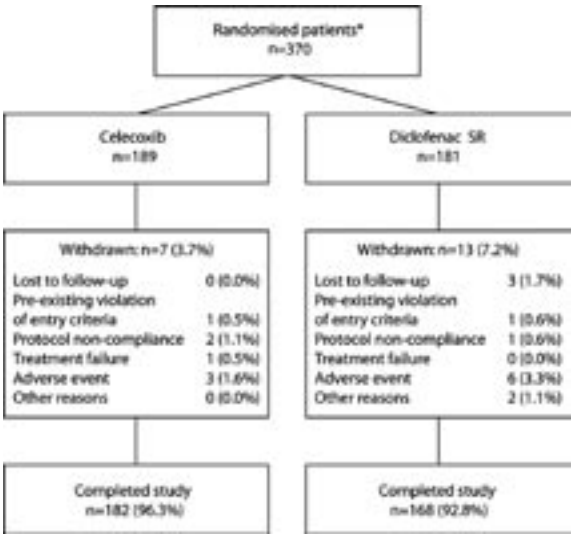

Fig. 1 Patient disposition.
*All patients were included in safety analyses. The modified intent-to-treat population included 366 patients. The per protocol analysis cohort included 346 patients.

Baseline patient characteristics were generally similar in both treatment groups (Table I). Patient ages ranged from 16 to 88 years, with a mean of approximately 31 years in each treatment group. The celecoxib group comprised 119 (63%) male and 70 (37%) female patients. A similar gender

Table I. Demographical and baseline injury characteristics (all randomised patients).

	Celecoxib 200 mg bid (n=189)	Diclofenac SR 75 mg bid (n=181)	p-value
Age (in years)			0.716
Mean ± SD	31.1 ± 11.2	31.5 ± 11.8	
Range	16 - 88	16 - 75	
Gender, n (%)			0.050
Male	119 (63%)	130 (72%)	
Female	70 (37%)	51 (28%)	
Race, n (%)			0.239
Caucasian	0 (0%)	1 (1%)	
Asian	189 (100%)	179 (99%)	
Other	0 (0%)	1 (1%)	
Duration of injury at time of first dose, (in hours)			0.312
Mean ± SD	15.2 ± 12.1	16.1 ± 12.4	
Range	1 - 48	0 - 48	
Activity causing injury, n (%)			0.988
Sport	90 (48%)	85 (47%)	
Non-sport	99 (52%)	96 (53%)	
Site of injury, n (%)			0.057
Left ankle	85 (45%)	99 (55%)	
Right ankle	104 (55%)	82 (45%)	
Type of injury, n (%)			0.555
Inversion	172 (91%)	173 (96%)	
Eversion	17 (9%)	8 (4%)	
Degree of sprain, n (%)			0.548
First	53 (28%)	56 (31%)	
Second	136 (72%)	125 (69%)	
Severity of pain (VAS), n (%)			0.833
Severe (>60 mm)	108 (57%)	106 (59%)	
Moderate (45 - 60 mm)	81 (43%)	75 (41%)	
Mild (<45 mm)	0	0	
Non-pharmacological therapy*, n (%)			
RICE	105 (55.6%)	88 (48.6%)	
Ankle taping/brace	32 (16.9%)	29 (16.0%)	
Crutches	17 (9.0%)	16 (8.8%)	
Cane	2 (1.1%)	2 (1.1%)	
Massage therapy	2 (1.1%)	0 (0.6%)	

*A patient could have more than one non-pharmacological treatment.

distribution was observed in the diclofenac group (72% of patients were male and 28% female). Time from injury to first dose of study medication was between 15 and 16 hours in both treatment groups.

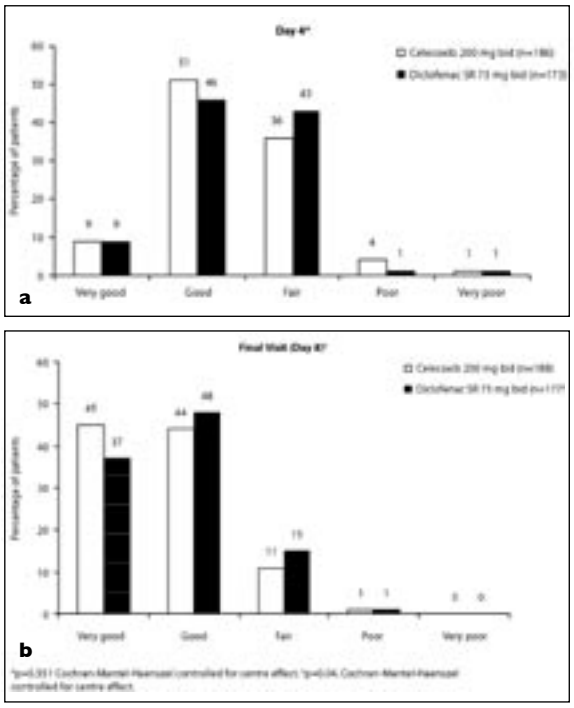

Fig. 2 Patient's global assessment of ankle injury for each treatment group (a) at day 4 (mITT population), and (b) at the final visit.

Most sprains were second degree in both treatment groups, and approximately 48% were sports-related. Non-pharmacological treatment, such as RICE and ankle taping, was prescribed similarly across groups (Table I).

Day 4 mean scores (PPA cohort) for patient's assessment of ankle pain VAS on full weight bearing decreased from 65 mm at baseline to 28 mm for the celecoxib group and from 66 mm to 30 mm for the diclofenac SR group (Table II). The difference between treatment groups was not statistically significant (p=0.618) and the upper bound 95% CI was 2.3 mm, supporting the non-inferiority of celecoxib versus diclofenac SR. Similar results were obtained for the mITT population.

For patient's assessment of ankle pain (VAS), the final visit VAS on full weight bearing was 13 mm for both treatment groups. The percentage of patients in the celecoxib and diclofenac SR treatment groups who improved by one or more grades between visits (responders) was 97% and 92%, respectively (p=0.047). Individual mean weighted average for pain VAS was 32 mm for both treatment groups for days 1 through 8.

Day 4 results of the patient's global assessment of ankle injury showed that the majority of patients rated their current injury status as fair or good (Fig. 2a). The percentage of patients who had improved by ≥1 grade from baseline was 88% and 83% for celecoxib and diclofenac SR treatment groups,

Table II. Patient's assessment of ankle pain VAS score (mm) on full weight bearing.

Assessment	Celecoxib 200 mg bid	Diclofenac SR 75 mg bid	Difference (celecoxib vs diclofenac SR)	
	n (mean±SD)	n (mean±SD)	LS mean	95% CI
Baseline	189	181		
	(65.4 ± 13.1)	(66.1 ± 14.0)		
Day 4*	182	164		
	(28.2 ± 16.3)	(29.5 ± 16.7)	-0.8	-3.9 to 2.3
Final visit	188	177†		
(Day 8 ± 1)	(12.8 ± 14.8)	(13.0 ± 13.6)	-0.2	-2.8 to 2.5

Note: All randomised patients at baseline, PPA population at day 4, mITT population at final visit.

* Primary end-point.

†One patient not included due to missing post-treatment VAS.

LS mean: least squares mean; CI: confidence interval; PPA: per-protocol analysis; mITT: modified intent-to-treat.

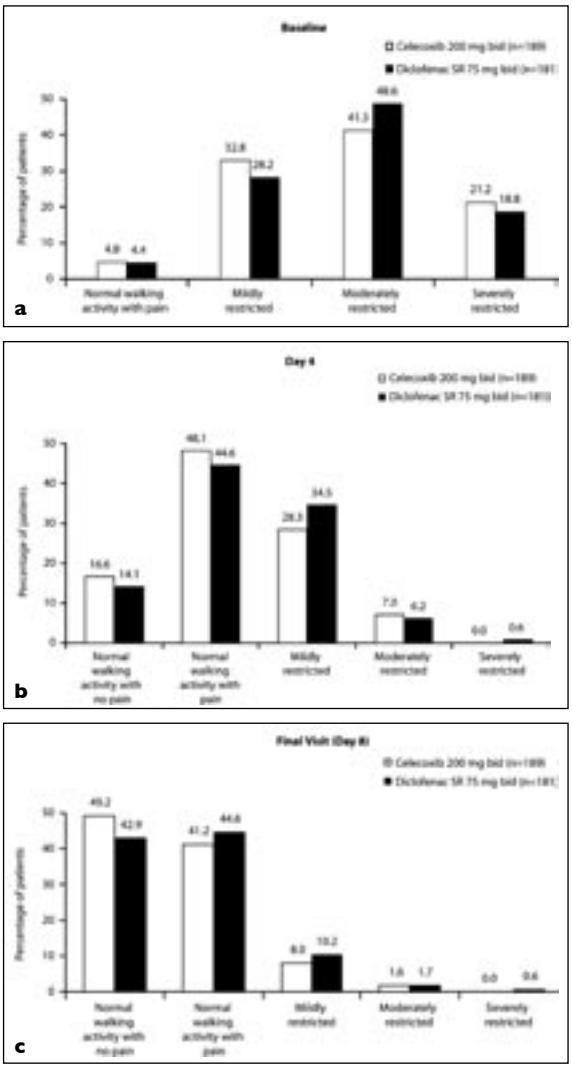

Fig. 3 Patient's global assessment of normal function/activity scores for (a) baseline, (b) day 4, and (c) final visit. No statistically significant differences were seen between treatment groups.

respectively. There was no statistically significant difference in the distribution of the patient's global assessment of ankle injury on day 4 between treatment groups (p=0.551).

Table III. Time to return to normal function/ activity (mITT population).

	Celecoxib 200 mg bid	Diclofenac SR 75 mg bid
Subjects who returned to normal function/activity		
Day 4	17%	14%
Day 9*	51%	46%
Subjects who returned to normal function/activity or improved by at least 2 grades		
Day 4	49%	49%
Day 9*	85%	80%
Subjects who returned to normal function/activity or improved by at least 1 grade		
Day 4	90%	89%
Day 9*	98%	97%

* Day 9 visit was used to make sure all allowable final visit days were included in the analyses.

At the final visit, scores were further improved, 89% of patients taking celecoxib and 85% of patients in the diclofenac SR group rated their current injury status as "good" or "very good," and the distribution of the patient's global assessment of ankle injury reached a statistically significant difference in favour of celecoxib (p=0.04) (Fig. 2b). At the final visit, the percentage of patients who had improved by ≥1 grade from baseline was 97% and 92% for the celecoxib and diclofenac SR treatment groups, respectively (p=0.047). The weighted average score over the eight-day treatment period was between "fair" and "good" for both treatment groups.

The percentage of patients returning to normal function/activity was similar between groups (Table III). By the final visit, approximately half of all patients had returned to normal function/activity (celecoxib, 51%; diclofenac SR, 46%). At baseline, 4.8% and 4.4% of patients reported normal walking

Table IV. Treatment-related adverse events occurring in ≥2% of patients in any treatment group.

Adverse event	Celecoxib (200 mg bid) (n=189)		Diclofenac SR (75 mg bid) (n=181)	
Patients with at least one treatment-related adverse event, n (%)	34	(18%)	30	(17%)
Abdominal pain	7	(4%)	6	(3%)
Headache	5	(3%)	5	(3%)
Somnolence	5	(3%)	5	(3%)
Dyspepsia	3	(2%)	7	(4%)
Dizziness	3	(2%)	5	(3%)
Rhinitis	3	(2%)	1	(1%)
Flatulence	2	(1%)	3	(2%)
Nausea	2	(1%)	3	(2%)

activity with pain in celecoxib and diclofenac SR groups, respectively (Fig. 3a). At day 4, 76% of patients in the celecoxib group and 79% of patients receiving diclofenac SR reported that their walking was mildly restricted due to pain or that their activity was normal but painful (Fig. 3B). By the final visit, 49% and 43% of patients reported normal walking activity with no pain in the celecoxib and diclofenac SR groups, respectively (Fig. 3c). The percentage of patients who had returned to normal function or had improved by ≥1 grade was 98% and 97% for celecoxib and diclofenac SR, respectively. There were no statistically significant differences between treatment groups.

The physician's global assessment of ankle injury scores were similar between treatment groups. Physicians rated the majority (approximately 87% in each treatment group) of ankle injuries as mild to moderate at the day 4 visit. By the final visit, 90% and 93% of ankle injuries were rated as mild and very mild in patients treated with celecoxib and diclofenac SR, respectively. The weighted average score over eight days was between mild and moderate for both treatment groups.

Patients and physicians reported similar satisfaction with both treatments. The mean score for celecoxib was 8.5 for both a patient's willingness to take the medication again and a physician's willingness to prescribe the drug. Diclofenac SR had a mean patient satisfaction score of 8.3 and a physician satisfaction score of 8.4. An additional subset analysis, which excluded patients with severe (medial) ankle sprain, confirmed the overall efficacy and safety findings (data not shown).

No serious adverse events occurred during the study. The most common adverse events were abdominal pain, headache, dyspepsia, and somnolence (Table IV). The majority of UGI events (specifically moderate or severe abdominal pain) were experienced by patients in the diclofenac SR group (2.2% vs 0.5% in the celecoxib group), although there was no statistically significant difference between treatment groups. A total of nine patients withdrew from the study due to adverse events (celecoxib, three; diclofenac SR, six). Six of these adverse events (celecoxib, one; diclofenac SR, five) were considered treatment related and were GI in nature.

DISCUSSION

This study was designed to parallel current clinical practice, and use of non-pharmacological therapies was permitted. For patients included in this study, approximately 50% of subjects in each treatment group also used RICE therapy. These data suggest that celecoxib can complement more traditional treatment strategies for rapid recovery following ankle injury. Our results suggest that celecoxib (400 mg loading dose followed by 200 mg bid for seven days) was at least as effective as diclofenac SR (75 mg bid for seven days) in ameliorating the signs and symptoms of acute first- or second-degree ankle sprain. Using standard efficacy measures, patients in both treatment groups had significantly decreased pain from baseline and a rapid return to normal function. While celecoxib and diclofenac SR were similar for all other end-points, the final visit scores for the patient's global assessment of ankle injury were statistically in favour of celecoxib (p=0.04), suggesting sustained symptomatic relief and rapid return to normal function.

These results observed in an Asian patient population support findings from a previous ankle sprain study conducted in patients of Latin American descent, where celecoxib was shown to be as effective as diclofenac 150 mg/d based on the patient's global assessment of ankle injury and patient's VAS scores[30]. The percentage of patients returning to normal function/activity by final visit was also similar – 59.5% for celecoxib and 61.7% for diclofenac[30]. Clinical studies have indicated that patients of diverse ethnic origins can differ in pain perception, reporting, and pain management[31-33]. The results of this study provide further data on the efficacy of celecoxib in diverse ethnic groups.

Celecoxib has also demonstrated similar efficacy to other non-COX-2 selective NSAID comparators in the treatment of ankle sprain. In a study comparing celecoxib 400 mg/d and naproxen

1000 mg/d, celecoxib was as effective as naproxen when measured by both the patient's assessment of ankle pain VAS and patient's global assessment of ankle injury[29]. Furthermore, celecoxib 400 mg/d has been demonstrated to be as effective as ibuprofen 2400 mg/d in the treatment of acute ankle sprain, with similar time to return to normal function and improvement in pain scores[28].

Without pharmacological treatment, ankle sprains generally heal within one to two weeks. However, inflammation associated with the injury may result in tissue damage and delayed return to normal function. Rehabilitation may be limited and the recovery period prolonged for patients who do not receive adequate therapy. Long-term ankle sprain studies show that pain and dysfunction can persist for over six months in a significant number of athletes (40%)[34,35]. A study in Asian athletes also demonstrated that as many as 73% had recurrent ankle sprains, of which 59% were associated with significant disability and impaired athletic performance resulting from initially inadequate treatment of the injury[36].

A multimodality treatment approach is recommended for acute ankle injuries, using RICE therapy[36] in conjunction with non-COX-2 selective NSAIDs[37-39] to manage acute pain while reducing inflammation. However, non-COX-2 selective NSAIDs inhibit COX-1, preventing the formation of constitutive prostaglandins necessary for various physiological functions, such as platelet aggregation[40,41]. Even after a single dose, non-COX-2 selective NSAIDs have been found to significantly inhibit platelet aggregation[24], and a number of studies have shown reduced platelet aggregation and elevated blood loss in healthy patients with non-surgical injuries treated with these agents[40,41]. Platelet aggregation is essential for the interruption of the ecchymosis that typically occurs with second-degree ankle sprains and is involved in wound healing. COX-2 selective inhibitors, which have COX-1-sparing properties, may offer an advantage over non-COX-2 selective NSAIDs in the treatment of acute ankle sprain, as they do not significantly affect platelet function[24]. In addition, COX-2 selective inhibitors have been shown to have a superior GI safety and tolerability profile compared with non-COX-2 selective NSAIDs even in the short-term[42-45]. In our study, both celecoxib and diclofenac SR were well tolerated over seven days and there were no statistically significant differences in the incidence of adverse events between treatment groups. However, a slightly higher percentage of patients treated with diclofenac SR reported UGI adverse events compared with those receiving celecoxib (2.2% vs 0.5%) and more patients in the diclofenac SR group withdrew from the study for adverse events compared with the celecoxib group. All treatment-related adverse events leading to discontinuation were GI in nature.

In the treatment of first- and second-degree ankle sprains in an Asian population, celecoxib (400 mg loading dose followed by 200 mg bid) was as effective as diclofenac SR (75 mg bid) as demonstrated by the patient's assessment of ankle pain VAS on day 4, the patient's and physician's global assessment of ankle injury, and the patient's assessment of normal function/activity. Further, the statistically significant superiority of celecoxib over diclofenac SR in the patient's global assessment of ankle injury at the final visit suggests sustained improvement with celecoxib. Due to its platelet-sparing properties and superior GI tolerability profile, celecoxib may offer an advantage over diclofenac SR in the management of acute ankle sprain injuries.

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