Randomised, open label, controlled trial of celecoxib in the treatment of acute migraine

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ABSTRACT

Introduction: Migraine is a common disabling condition that results in considerable socioeconomic loss. The role of non-steroidal anti-inflammatory drugs (NSAIDs) in acute migraine has been well-established. We compared the efficacy of the cyclooxygenase-2 inhibitor celecoxib with the NSAID, naproxen sodium, in the treatment of acute migraine.

Methods: This was a randomised, open label, controlled trial. We selected patients with a diagnosis of migraine, based on the International Headache Society revised criteria. 60 patients were randomised to either celecoxib 400 mg (30 patients) or naproxen sodium 550 mg (30 patients). Patients took the study medicine for the first acute migraine episode that occurred during the study period and reported the headache reduction based on a visual analogue score (VAS). Patients were reviewed after a month to check on VAS at one and two hours, compared to the baseline. Any side effects of the medication were also recorded.

Results: Of the 52 patients who completed the study, eight did not experience any headaches. The mean VAS in the celecoxib group improved significantly from baseline (6.48 +/- 1.53) to one hour (4.28 +/- 2.11) and two hours (2.24 +/- 2.57) (p-value is less than 0.0005). The mean VAS in the naproxen sodium group also improved significantly from baseline (7.30 +/- 1.66) to one hour (4.81 +/- 2.50) and two hours (2.63 +/- 2.65) (p-value is less than 0.0005). However, there was no significant difference between the magnitudes of improvement between the treatment groups. The incidence of gastric pain was significantly higher in the naproxen sodium group (p-value is equal to 0.029).

Conclusion: In comparison with naproxen sodium, celecoxib was equally effective in relieving pain in acute migraine and caused significantly less gastric pain.

Keywords: acute migraine, celecoxib, drug side-effects, gastric pain, migraine, naproxen sodium, visual analogue score

Singapore Med J 2007; 48(9):834–839

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INTRODUCTION

Migraine is a common, disabling condition that results in considerable social and economic losses.[1] The pathophysiological process of the attack is presumed to occur via the trigemino-vascular pathway and other systems that interact with intra- and extracranial vasculature and perivascular spaces.[2,3] Centrally-mediated prostaglandins are involved in the pathological amplification and exaggeration of the pain pathway, hence its pivotal role in causing acute migraine. The central role of prostaglandins (PGs) may provide a common denominator in several hormonal, neural and various other influences on the blood vessels for the pathophysiology of acute migraine attacks. The possible role of PG-associated inflammation may be countered with non-steroidal anti-inflammatory drugs (NSAIDs), as well as selective enzyme cyclooxygenase (COX-2) inhibitors.[4,5] The up-regulation of COX-2 in the central nervous system in response to inflammation is not associated with an increase in COX-1. Selective inhibition of COX-2 within the brain is thus a rational strategy to counteract this process.

The use of naproxen sodium in acute migraine has been well established. It abolishes the PG-associated inflammation centrally. It is a commonly-prescribed first line treatment for acute migraine because of its low cost and proven efficacy.[4,5] Pradalier et al reported its usefulness in acute migraine treatment. [6] They compared naproxen sodium with ergotamine in 114 patients. Naproxen sodium has been more effective in reducing headache severity, nausea, vomiting and light-headedness. In that trial, a relatively high dose of naproxen sodium (750–1,250 mg) was used. It can be easily absorbed and achieve therapeutic concentrations after 20–30 minutes and maximum

Table I. International Headache Society revised criteria for migraine.[17]

Diagnostic criteria
A. At least five attacks fulfilling the criteria B–D.
B. Headache lasting 4–72 hours and occurring < 15 days/month (untreated or unsuccessfully treated).
C. Headache has at least two of the following characteristics:
• Unilateral localisation.
• Pulsating quality.
• Moderate or severe intensity (inhibits or prohibits daily activity).
• Aggravation by or causing avoidance of routine physical activity (i.e., walking or climbing stairs).
D. During headache, at least one of the following:
• Nausea and/or vomiting.
• Photophobia and phonophobia.
E. Not attributed to another disorder.

Table II. International Headache Society revised criteria for typical aura with migraine headache. [17]

A. At least two attacks fulfilling criteria B–D.
B. Aura consisting of at least one of the following, but no motor weakness:
1. Fully reversible visual symptoms including positive features (e.g., flickering lights, spots, or lines) and/or negative features (i.e., loss of vision).
2. Fully reversible sensory symptoms including positive features (i.e., pins and needles) and/or negative features (i.e., numbness).
3. Fully reversible dysphasic speech disturbance.
C. At least two of the following:
1. Homonymous visual symptoms and/or unilateral sensory symptoms.
2. At least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes.
3. Each symptom lasts ≥ 5 and ≤ 60 minutes.
D. Headache fulfilling criteria B–D (Table I) begins during the aura or follows aura within 60 minutes
E. Not attributed to another disorder

concentration two hours after ingestion. Its biological half-life is 12–15 hours. Our usual practice is to prescribe naproxen sodium at a dose of 550 mg; this appears to be the effective tolerable dose, although there is no conclusive evidence to support this in our local population.

Ergotamine, a specific migraine treatment, causes nausea, vomiting and dependence. Sumatriptan, a 5-hydroxytryptamine agonist is effective against acute attacks but is costly. Prophylactic medication usually leads to weight gain and sedation. These side effects lead to poor compliance, especially in young patients and the working class.[7,8] Prescribed at therapeutic doses, the selective COX-2 inhibitors are expected to offer the same anti-inflammatory benefits as the NSAIDs, with a lower risk of serious gastrointestinal (GI) adverse reactions.[9,10] Rofecoxib has been shown to be effective in acute migraine.[11] However, celecoxib has been reported to be effective in non-migrainous headaches.[12] The aim of the study was to compare the efficacy of the COX-2 inhibitor, celecoxib, with the NSAID, naproxen sodium, in the treatment of acute migraine.

METHODS

This was a prospective, randomised, open label, comparative study. 60 patients with migraine were recruited from the neurology outpatient clinic in Hospital Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia, from December 2004 to March 2005. The patients were not naproxen sodium or celecoxib naïve, this factor was considered if there was drug tolerance and or unresponsiveness to the trial medication in acute migrainous headache. The patient selection criteria included those who were older than 18 years, had disease duration of at least six months, and had an attack frequency of at least twice per month over the past six months. We excluded those who had underlying organic causes for headaches, previous adverse reaction to NSAIDs, pregnant and lactating women, and patients with known contraindications to the use of NSAIDs.

The diagnosis of migraine was based on the International Headache Society revised criteria for migraine 2004 (Tables I and II). We used a visual analogue

Table III. Baseline demographical and clinical characteristics of migraine patients taking celecoxib or naproxen sodium.

	Celecoxib 400 mg (%) n = 25	Naproxen sodium 550 mg (%) n = 27	Chi-square value	p-value*
Age (years)				
Mean	33.0	32.0	27.63	0.37
SD	10.2	10.8		
Gender				
Female	18 (72.0)	21 (77.8)	0.231	0.631
Male	7 (28.0)	6 (22.2)		
Ethnicity				
Malay	20 (80.0)	18 (66.7)		
Chinese	3 (12.0)	7 (25.9)	1.631	0.442
Indian	2 (8)	2 (7.4)		
Education				
Non-tertiary	10 (40)	16 (59.3)	1.92	0.165
Tertiary	15 (60)	11 (40.7)		
Migraine				
With aura	14 (63.0)	17 (63.3)	0.26	0.609
Without aura	11 (37)	10 (36.7)		
Duration of migraine since onset (years)				
Mean	10	8	13.00	0.836
SD	9.3	9.5		
Frequency of attacks				
1–5	19 (76)	25 (92.6)		
6–10	5 (20.0)	0	6.08	0.048
>10	1 (4)	2 (7.4)		
Prophylactic medication				
Pizotifen	7 (28)	6 (22.0)		
Amitriptyline	2 (8)	3 (11.7)		
Propranolol	4 (16)	2 (7.4)	4.258	0.513
Flunarizine	1 (4)	0		
Others	1 (4)	0		
None	10 (40)	16 (59.3)		

* Significant at $p < 0.05$

scale (VAS) to assess pain severity, and considered VAS with a standard deviation of 17 mm and the minimal clinical difference of 13 mm. This allowed the detection of a statistically significant 25% difference in headache relief between celecoxib and naproxen sodium with a power of 80%, an alpha risk of 5% and a drop out rate of 20%. A sample size of 55 patients was required based on Altman's normogram. There were 60 envelopes, each concealed a piece of paper with a code number, out of which 30 were numbered C1 to C30 and the remaining, S1 to S30. The patients were then instructed to pick an envelope at random. The patients who selected the envelope containing the code C was given Celebrex (Celecoxib 400 mg) and S were given Synflex (Naproxen sodium 550 mg) accordingly. The patients were instructed to take the study medications at the onset of their migraine attacks and to score the severity of the attack at baseline, one hour and two hours after ingestion of the medication. The scores were documented on the VAS sheet. Any side-effects and rescue medication needed were also entered on the same sheet. The patients were then reassessed four weeks later. Rescue medication consisted of the patient's usual migraine medication. Once the rescue medication was used, these patients were disqualified from further analysis, because the pain scoring would be affected and the results would then not be representative of the therapeutic effect of the trial drugs.

The use of prophylactic medication on a constant dosing regimen was allowed. The prophylactic medications used included amitriptyline, propranolol,

Table IV. Comparison of visual analogue scores between the celecoxib and naproxen sodium groups.

	Celecoxib 400 mg n = 25	Naproxen sodium 550 mg n = 27	Independence *t*-test	p-value
Baseline	6.48 ± 1.531	7.30 ± 1.660	1.839	0.072
First hour	4.28 ± 2.112	4.81 ± 2.497	0.831	0.410
Second hour	2.24 ± 2.570	2.63 ± 2.648	0.538	0.407

Table V. Adverse events reported by patients.

	Celecoxib (%) n = 25	Naproxen sodium (%) n = 27	Pearson chi-square value	p-value*
Epigastric pain	1 (4)	7 (26.0)	4.794	0.029
Nausea	1 (4)	0	1.101	0.299
Numbness	1 (4)	1 (3.7)	0.003	0.956
Drowsiness	0	1 (3.7)	0.944	0.331
Insomnia	0	1 (3.7)	0.825	0.364

* Significant at $p < 0.05$

pizotifen, flunarizine, other calcium channels blockers, and oral contraceptive pills. We measured the breakthrough headache pains and selected those with at least two attacks in a month despite prophylactic medication. Those who had no or very mild migrainous headache were excluded.

The data was analysed using the Statistical Package for Social Sciences, version 11.0 (SPSS Inc, Chicago, IL, USA), and a p-value of less than 0.05 were deemed to be statistically significant. Parametric analysis was used. Numerical data was expressed as mean ± standard deviation (SD). Student paired *t*-test was used to compare the means within each group. The independent *t*-test was used to compare the mean between two groups. The study was approved by the Medical Research and Ethics Committee of the Medical Faculty, Universiti Kebangsaan Malaysia. (Ethics Committee Approval Code: FF-72-2004).

RESULTS

60 patients with migraine, with and without aura, were recruited. The mean age was 33 ± 10.2 years for the celecoxib group, and 32 ± 10.8 years for the naproxen sodium group. The distributions of the patients and their clinical characteristics are shown in Table III. Of the 60 subjects enrolled in the study, half were randomly assigned to receive celecoxib 400 mg (Celebrex) and the remaining half naproxen sodium 550 mg (Synflex). Eight patients (15%) did not take the study medication, because either they did not experience any attacks or the attacks were mild. The remaining 52 subjects who took the study medication were included in the intent-to-treat analysis, with 25 in the celecoxib group and 27 in the naproxen sodium group. Out of the 60 patients, 31 (52%) had migraine with aura. The mean duration of migraine since onset in the celecoxib group was longer (10 years versus 5.5 years) and frequency of migraine attacks was lower (less than five times per month) compared to the naproxen sodium group (19 [76%] versus 25 [92.6%]). 15 patients in the celecoxib group were on prophylactic medication for migraine compared to 11 in the naproxen sodium group, but those agents did not significantly alter the outcome on the VAS.

In the celecoxib group, the VAS were 6.48 ± 1.53 at baseline, 4.28 ± 2.11 at one hour, and 2.24 ± 2.57 at two hours. In the naproxen sodium group, the VAS at baseline, one hour and two hours were 7.30 ± 1.66, 4.81 ± 2.50, and 2.63 ± 2.65, respectively (Table IV). In the celecoxib group, two patients (8.0%) achieved pain freedom at one hour and ten patients (40.0%) at two hours. This was comparable to the naproxen sodium group where two patients (7.7%) achieved total headache relief at one hour, and eight patients (30.8%) were symptom-free at two hours. In the intergroup analysis, there was no significant difference between both groups in VAS at baseline to one hour ($p = 0.410$) and at baseline to two hours ($p = 0.407$) (Table IV). The results were adjusted for differences in baseline characteristics between the two groups. The side-effects that were reported by the patients included epigastric pain, drowsiness, nausea, numbness and insomnia. Among all the reported side effects, only the incidence of epigastric pain was significantly higher in the naproxen sodium group ($p = 0.029$) (Table V).

DISCUSSION

52 patients completed the study; the remaining eight did not experience any headaches during the study period. The mean VAS in the celecoxib group improved well from baseline (6.48 ± 1.53) to one hour (4.28 ± 2.11) and two hours (2.24 ± 2.57) ($p < 0.0005$). The mean VAS in

the naproxen sodium group also improved from baseline (7.30 ± 1.66) to one hour (4.81 ± 2.50) and two hours (2.63 ± 2.65) ($p < 0.0005$). There was no significant difference between the magnitudes of improvement between the treatment groups. The incidence of gastric pain was significantly higher in the naproxen sodium group ($p = 0.029$). Migraine patients are of ten young adults who are active in life, either studying or working. In our study, the majority of the patients belonged to the 20–29 years age group. The majority of patients were young women (75%). The female-to-male ratio for migraine has been previously reported to be in the order of 3:1.[1]

Abortive treatment, whether migraine specific and non-specific, is generally required to treat the acute migraine attack. The migraine-specific agents include ergotamine, dihydroergotamine and the triptans.[7,8] The cheaper and more easily available form of abortive non-migraine specific agent is a NSAID. The rationale for using NSAIDs in the treatment of migraine is based on the possible involvement of PG in the pathophysiology of migraine. NSAIDs exert their action by inhibiting the COX enzyme, and thereby decreasing the synthesis of PGs and leukotrienes from arachidonic acid. They prevent neurologically-mediated inflammation in the trigeminovascular system.[5] We now know that COX consists of two isoenzymes. COX-1 is constitutively expressed and generates PGs believed to be involved in GI mucosal protection, while COX-2 is induced at sites of inflammation throughout the body. The risk of gastric mucosa erosion is high with NSAIDs that are nonselective-COX inhibitors.[11,12]

The efficacy of NSAIDs in acute migraine treatment has been proven in a few clinical trials. Based on the class effect of NSAIDs, selective COX-2 inhibitors could exert its pain-relieving properties in migraine and yet produce a lower incidence of GI disturbances. In Malaysia, celecoxib is the only approved COX-2 inhibitor. It is relatively safe for short-term use on a "when needed only" basis. There have been no trials so far using celecoxib in the treatment of acute migraine, but there were a few case reports on the use of celecoxib for other forms of headaches.[11] In the present study, we have shown that celecoxib, at a dose of 400 mg taken during acute migrainous headaches, is as effective as naproxen sodium in pain relief. The majority of the study patients did not wait to take the medication after a meal as advised, as most of the attacks occurred acutely and quick pain relief was required. The complaint of numbness of the limbs, nausea and drowsiness did not differ significantly between the groups. One patient reported having insomnia after naproxen sodium, which did not occur when he was on mefenamic acid previously. The occurrence of epigastric pain was significantly less in the celecoxib group. Only one patient who took celecoxib on an empty stomach reported a brief episode of epigastric discomfort.

In September 2004, Merck withdrew rofecoxib from the market because of unexpected increased cardiovascular toxicity in a trial, designed to test the hypothesis that COX-2 inhibitors could prevent recurrent colonic polyps.[13] The increase in cardiovascular risk began after 18 months of treatment with rofecoxib. The Colorectal Adenoma Prevention with Celecoxib Study showed that celecoxib at either 200 mg or 400 mg twice a day, 2.8 to 3.1 years after treatment, had a relative risk of 2.8 for cardiovascular events.[14] Another COX-2 inhibitor, valdecoxib, and its intravenous form parecoxib, has increased incidence of cardiovascular events, in patients who have undergone coronary artery bypass surgery. These high-risk patients were given intravenous parecoxib for three days, before switching to valdecoxib for the next ten days.[15]

It has been recommended that COX-2 inhibitors should be avoided in patients undergoing coronary artery bypass graft. Thromboxane A2, a major COX-1-mediated product of metabolised arachidonic acid causes irreversible platelet aggression, vasoconstriction, and smooth muscle proliferation, whereas prostacyclin, an inhibitor of platelet aggregation and a vasodilator, causes inhibition of smooth-muscle proliferation. COX-2 is the chief source of systemic prostacyclin synthesis, and COX-2 inhibitors may increase the cardiovascular risk by shifting the functional balance of these vasoactive eicosanoids.[10,16] However, in our study, celecoxib was used in a relatively small dose and for a short duration. Our target population was relatively young with low cardiovascular risk. It is safe if used according to FDA recommendations. So far, all the previous acute migraine treatment trials compared NSAIDs with a placebo or other migraine-specific agents, such as triptans or ergotamines. Silberstein et al reported the effects of different doses of rofecoxib with a placebo.[11] They found that rofecoxib was beneficial for acute migraine pain relief within two hours. In our study, we compared celecoxib and naproxen sodium, which to the best of our knowledge, has never been reported before for acute migraine treatment.

The study limitations were that there was no placebo arm, and the follow-up period was limited. We were not able to blind the study because of ethical issues relating to the use of placebo in migraine. The substantial evidence that celecoxib is a useful migraine drug has been considerably weakened by the withdrawal of some COX-2 inhibitors from most markets. As such, celecoxib is seldom used by most neurologists to treat acute migraine. However, in some circumstances where the likelihood of patients developing NSAID-induced gastritis is high, celecoxib may be a useful alternative. We conclude from our study that celecoxib in a dose of 400 mg during an acute migraine attack can achieve the same efficacy as

naproxen sodium 550 mg. Celecoxib is an alterative mode of therapy in acute migraine treatment, and compared to naproxen sodium, is less likely to cause epigastric pain. The limitations of the present study call for a larger, randomised, double-blind trial.

ACKNOWLEDGEMENT

We would like to thank the Dean of the Medical Faculty at the Universiti Kebangsaan Malaysia for allowing us to publish this paper.

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