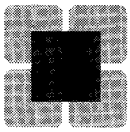

Flurbiprofen in the prophylaxis of migraine

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■ Flurbiprofen, a nonsteroidal anti-inflammatory drug with effects on prostaglandin synthesis, platelet serotonin release, and beta-endorphin, was studied for efficacy in migraine prophylaxis. Twenty-three patients completed the 20-week, placebo-controlled, double-blind, crossover trial. Flurbiprofen, in a dose of 100 mg twice daily, and placebo were each given for 8 weeks, with a 2-week "washout" period between the treatment periods. Flurbiprofen significantly reduced migraine intensity ($P < .05$), total hours with migraine ($P < .015$), and the dosing frequency of relief medication ($P < .015$). Total hours with migraine decreased by 41%, and the use of relief medication decreased by 31%. The reduction in migraine frequency did not reach statistical significance ($P < .10$). Adverse effects were infrequent. Based on the overall improvement in migraine parameters, flurbiprofen can be recommended for use in migraine prophylaxis.

□ INDEX TERMS: FLURBIPROFEN; MIGRAINE □ CLEVE CLIN J MED 1993; 60:43–48

MIGRAINE HEADACHE represents a common disorder with an estimated prevalence of 41 per 1,000 in the United States.[1] Migraine is a frequent source of absenteeism and decreased productivity, costing American business an estimated $4.5 billion per year.[2] Beyond societal costs, individual suffering is significant. Migraine patients consume more tranquilizers, amphetamines, and sleeping pills than headache-free controls.[3]

Currently available prophylactic treatment for migraine consists primarily of beta blockers, calcium-channel blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, and methysergide. While these agents are useful, they are not uniformly effective and are associated with side effects.

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WHAT CAUSES MIGRAINE?

The pathophysiology of migraine is not completely understood and is probably multifactorial. The initial event in migraine appears to involve the release of serotonin,[4] either from platelet stores, the dorsal raphe nucleus, or both. Nociceptive transmission takes place through sensory branches of the trigeminal nerve,[5] which terminate within the smooth muscle of cerebral blood vessels. The sensory axons trigger release of vasodilating and permeability-promoting peptides,[6] with the production of a vascular inflammatory response—the so-called "sterile arteritis" described by Wolff.[7]

Raskin states that the cardinal abnormality of migraine is the defective modulation of serotonin release.[4] Platelet activity in migraine sufferers differs from controls,[8,9] with chronic aggregation and increased platelet adhesiveness during the headache phase of migraine. The aggregated platelets release vasoactive prostaglandins and serotonin. Prostaglan-

din E_1 causes dilatation of the external carotid arteries, while prostaglandin F_2 induces intracerebral vasoconstriction.[10]

Sicuteri has proposed a theory of migraine pathophysiology that suggests that substance P takes part in nociceptive transmission within the trigeminal system.[5] Substance P induces vasodilation, plasma extravasation, and nasal and conjunctival congestion. Endogenous opioids inhibit the release of substance P from primary sensory neurons.[5] Drugs that affect beta-endorphin and methionine enkephalin (met-enkephalin) may control both the abnormal pain response and vascular changes of migraine.

Moskowitz[11] has shown acute inflammatory changes, including vasodilation and plasma extravasation, in the cerebral arteries during stimulation of the trigeminal nerve. This suggests that stimulation of the trigeminovascular complex induces a sterile arteritis that is the final common pathway of migraine.

BASIS FOR TREATMENT WITH NSAIDS

NSAIDs act to inhibit inflammation through their effects on chemotaxis, phagocytosis, lysosomal enzyme release, kinin generation, complement generation, and formation of prostaglandins.[12] Furthermore, certain NSAIDs act as analgesics through central pain mechanisms. These most likely involve mediation of substance P, beta-endorphin, and met-enkephalin.[13] As these activities all affect the proposed pathway of migraine, it is logical to evaluate NSAIDs in migraine prophylaxis.

Several NSAIDs have been reported to have prophylactic activity in migraine. Among these are aspirin,[14] naproxen,[10,15–17] ketoprofen,[18] flufenamic acid,[19] tolfenamic acid,[20] and fenoprofen calcium.[21]

Flurbiprofen, an NSAID derived from propionic acid, has several unique properties that suggest potential benefit in migraine prophylaxis. Flurbiprofen can inhibit platelet serotonin release[22] and increase levels of beta-endorphin,[23] and it may alter tissue levels of immunoreactive bradykinin.[24] These actions theoretically allow flurbiprofen to prevent migraine attacks at the level of platelet serotonin release, trigeminal nociception, and cerebrovascular inflammation.

In addition, Awidi[25] studied flurbiprofen in the acute treatment of migraine and found it to be effective. Other NSAIDs that have been effective in acute treatment, including naproxen sodium[26] and aspirin,[27] have also been effective in migraine prophylaxis.

We investigated the efficacy and safety of flurbiprofen in the prophylaxis of migraine in a controlled trial.

PATIENTS AND METHODS

The trial design was a double-blind, randomized, placebo-controlled, crossover of 20 weeks' duration. Flurbiprofen dosage was 100 mg twice daily. Patients who had migraine with aura, without aura, or both, as diagnosed using International Headache Society criteria,[28] were included. All patients had migraine for at least 2 years, with between two and eight migraine attacks during the previous month. A previous attempt at migraine prophylaxis with drugs was not cause for exclusion. Patients with cluster headache or frequent tension-type headaches were excluded, as were those with a history of aspirin or NSAID sensitivity, drug abuse, alcoholism, and renal, hepatic, or cardiac disease. Patients using other NSAIDs or migraine prophylactic drugs were also excluded.

The study was approved by the Cleveland Clinic Foundation Institutional Review Board. Written informed consent was obtained from each participant.

The study design included a 2-week single-blind placebo "washout" period, followed by an 8-week double-blind treatment period. Patients then underwent a 2-week single-blind placebo washout to lessen the likelihood of crossover pharmacologic effects of flurbiprofen. A second 8-week double-blind crossover treatment period then followed. Throughout the study, patients were interviewed at 4-week intervals during treatment periods and every 2 weeks during washout periods.

A laboratory evaluation that included complete blood count, urinalysis, and chemistry profile (SMA 16) was obtained at the screening visit and again at the end of both treatment periods. Urine pregnancy test was performed at the screening visit for female patients. Stool was tested for occult blood every 4 weeks during treatment periods.

Patients were required to keep a daily diary, which was used to assess therapeutic efficacy. This diary measured the following for each headache: time of onset; severity (on a scale of 1 to 5: 1, no limitation in daily activity; 2, some limitation; 3, moderate limitation; 4, severe limitation; 5, bedridden); duration of headache; when and if concomitant relief medication was taken; and any other health changes. This permitted examination of five parameters: migraine frequency, migraine severity, total hours with migraine, relief medication dosing frequency, and adverse effects.

Data were analyzed using two-tailed tests and two-way analysis of variance (ANOVA) fixed-effects model for a two-period crossover design, using the statistical package SAS. Power calculations determined a sample size of 12 patients in each treatment sequence (total 24 patients) would be able to detect a reduction of 50% or more in the mean number of headaches observed in an 8-week period. For the measurement of migraine frequency, a single migraine attack was defined as preceded and followed by 8 hours awake and headache-free. A $P < .05$ was regarded as significant and, a $P < .10$ was regarded as marginally significant. Some clinicians consider an improvement of 50% or greater of any parameter (compared with placebo) as the best marker for clinical effectiveness.[29] This was determined for all parameters except intensity.

TABLE 1
EFFICACY OF FLURBIPROFEN VS PLACEBO IN MIGRAINE

Study variable	Flurbiprofen (mean ± SD)	Placebo (mean ± SD)	*P* value
Flurbiprofen first			
Migraine frequency (attacks/8 weeks)	4.4 ± 2.7	5.6 ± 3.2	
Migraine duration (hours/8 weeks)	64.2 ± 40.2	104.0 ± 100.0	
Relief medication dosing frequency (doses/8 weeks)	10.7 ± 7.1	13.7 ± 8.8	
Placebo first			
Migraine frequency	4.3 ± 4.1	5.8 ± 3.6	
Migraine duration	41.4 ± 43.2	74 ± 39	
Relief medication dosing frequency	8.7 ± 8.9	14.3 ± 12.7	
Means			
Migraine frequency	4.39	5.73	*P*< .10
Migraine duration	51.7	87.6	*P*< .015
Relief medication dosing frequency	9.7	14.0	*P*< .015

SD, standard deviation

TABLE 2
EFFECT OF FLURBIPROFEN ON FREQUENCY OF MIGRAINE ATTACKS (NUMBER OF ATTACKS)

Flurbiprofen first			Placebo first		
Washout	(2 weeks)	1.8	Washout	(2 weeks)	2.1
Flurbiprofen	(8 weeks)	4.4 ± 2.7	Placebo	(8 weeks)	5.8 ± 3.6
Washout	(2 weeks)	2.1	Washout	(2 weeks)	1.1
Placebo	(8 weeks)	5.6 ± 3.2	Flurbiprofen	(8 weeks)	4.3 ± 4.1

Patients were instructed to avoid all NSAID- and aspirin-containing drugs. Relief medication was limited to a hydrocodone-acetaminophen compound or an isometheptene-acetaminophen preparation. Patients who did not obtain relief with either of those drugs were allowed to use ergotamine tartrate-caffeine compounds.

Thirty-one patients enrolled in the initial washout period. Two patients dropped out during the washout period, and 29 patients entered the first randomized treatment period. Four patients dropped out during the first treatment period, and two dropped out after the first treatment period. Only two patients dropped out because of side effects (abdominal pain and burning).

Twenty-three patients completed the protocol (4 men, 19 women). Their mean age was 36 (range 19 to 49). The mean duration of migraine history was 17 years (range 4 to 35). Nineteen patients had migraine without aura, two had migraine with aura, and two had migraine with and without aura. There were no significant demographic differences between the group receiving flurbiprofen first and the group receiving placebo first.

RESULTS

Three of four effectiveness parameters showed the superiority of flurbiprofen compared with placebo (*Table 1*). Migraine intensity ($P < .05$), total hours of migraine ($P < .015$), and use of relief medication ($P < .015$) showed statistically significant benefits with flurbiprofen, while migraine frequency ($P < .10$) showed a trend toward benefit.

Migraine frequency fell from 5.73 attacks per 8 weeks on placebo to 4.39 attacks per 8 weeks on flurbiprofen ($P < .10$) (*Table 2*). This represents a 23% decrease in migraine frequency. Sixteen of 23 patients (70%) had a decrease in migraine frequency during treatment with flurbiprofen, with 10 patients (43%) noting a 50% or greater reduction in migraine frequency. Fifteen of 23 patients had a 25% or greater decrease in migraine frequency. Seven patients had fewer headaches while on placebo.

Migraine intensity was determined using a scale of 1 to 5, as described above, to measure the limitation in

daily activities. Migraine intensity during placebo treatment averaged 2.5, compared with 2.1 during flurbiprofen treatment ($P < .05$).

Total hours with migraine (duration) were available for evaluation for 20 of 23 patients, as three patients did not fill out their diaries adequately to measure this parameter. Total hours with migraine fell from 87.58 hours per 8-week period on placebo to 51.66 hours per 8-week period on flurbiprofen ($P < .015$). This represents a 41% drop in the number of hours patients suffered from migraine. Fifteen of 20 patients (75%) had a decreased total duration of migraine. Seven of 15 (47%) had a 50% or greater reduction in migraine duration. Five of 20 patients had a decrease in migraine duration with placebo, with one patient noting a 50% or greater reduction in total hours with migraine.

The prescribed relief drugs had different initial doses: the isometheptene-acetaminophen preparation had an initial dose of two capsules, while the hydrocodone-acetaminophen compound had an initial dose of one tablet. We elected to measure the dosing frequency of the relief medication, rather than the total number of tablets or capsules taken. The dosing frequency of relief medication per 8-week period was 14.0 in the group receiving placebo and 9.7 in the group receiving flurbiprofen ($P < .015$). This represents a 31% decline in relief medication dosing frequency. Fourteen patients had less frequent relief medication use with flurbiprofen; six patients had less frequent relief medication use with placebo; and three patients had the same dosing frequency during both treatment periods. Nine patients (39%) had a 50% or greater reduction in relief medication dosing frequency during flurbiprofen treatment.

Five of 31 enrolled patients reported adverse effects related to medication. As expected with NSAIDs, the majority of adverse effects involved gastrointestinal symptoms. In two patients, stool testing found occult blood. One patient had a 1.9-g drop in hemoglobin, and one patient had a small drop in hematocrit. Other problems included abdominal cramps with diarrhea (one patient), cold sores in the mouth (one patient), and epigastric pain with emesis (one patient). Blood chemistry testing revealed no significant drug-related abnormalities.

DISCUSSION

The results of this study provide evidence of a definite effect of flurbiprofen in the prophylaxis of migraine. Favorable effects were most notable for a 41% reduction in total hours with migraine and a 31% reduction in the dosing of relief medication.

Controlled trials in migraine prophylaxis have been conducted on several NSAIDs.[30] Although most of the studies were conducted as blinded crossover trials, the data were often presented as derived indices or scores, and, unfortunately, this prevents direct comparisons between studies. Indomethacin was studied in 1968[31] but was found ineffective. Ketoprofen[18] was found to be mildly effective, with a 23% mean reduction of "headache index" and an 18% mean reduction in "headache days." Headache index was reduced by 50% or more in 21% of patients. Naproxen[15] 250 mg twice daily showed slight benefit compared with placebo. Naproxen sodium 550 mg twice daily has been shown to have significant benefit in two trials. Welch[16] reported that migraine severity fell 39%. Severity was decreased in 77% of his patients, with 32% noting a 50% or greater improvement. Migraine duration was reduced by 19%, with 74% of patients noting benefit and 32% having a 50% or greater reduction in duration. Ziegler[10] reported a 27% decrease in severity, a 28% reduction in migraine duration, and a 24% decline in the use of relief medication, based on the use of naproxen sodium 550 mg twice daily. Diamond[21] evaluated fenoprofen 600 mg three times daily and reported that 36% of patients had a 50% or greater improvement in "headache unit index." In Mikkelsen and Folk's study[20] with tolfenamic acid, 45% of patients had a 50% or greater reduction in migraine frequency.

Aspirin has also been evaluated as a migraine prophylactic agent.[14] With a dose of 650 mg twice daily, 75% of patients noted a 50% or greater reduction in frequency of attacks. Although these studies cannot be directly compared, flurbiprofen 100 mg twice daily appears to be comparable with naproxen sodium 550 mg twice daily and is probably superior to most other NSAIDs in migraine prophylaxis.

Flurbiprofen's mechanism of action in migraine prophylaxis is unknown. Flurbiprofen is unique among NSAIDs: it is a potent inhibitor of prostaglandin synthesis and a potent analgesic.[13] It is unlikely that its effect on migraine is purely mediated by peripheral mechanisms such as prostaglandin or platelet inhibition. Indomethacin, a potent inhibitor of prostaglandin synthesis,[13] has little effect on migraine prophylaxis,[31] while naproxen sodium, a weak inhibitor of prostaglandin synthesis,[13] is quite effective in migraine prophylaxis.[10,16] Welch[16] found no correlation between the degree of platelet inhibition induced by NSAIDs and their efficacy in migraine prophylaxis.

NSAIDs probably effect migraine through central mechanisms. Gaucher et al noted that NSAIDs achieve measurable levels in cerebrospinal fluid.[32] Bensemanna and Gascon[33] proposed that analgesia from the NSAID sodium salicylate correlated with the increase in turnover of serotonin, norepinephrine, and dopamine in the brain stem. Additionally, some NSAIDs have been reported to reduce the firing discharge of thalamic neurons that were evoked by noxious stimuli.[34,35] These studies provide evidence for the hypothesis that serotoninergic mechanisms, dopaminergic mechanisms, or both may be relevant to NSAID-mediated antinociception. Antinociception within the trigeminovascular system probably leads to effective migraine prophylaxis.

NSAIDs also block neurogenic inflammation in the dura mater.[36] High-dose indomethacin and high-dose aspirin reduce plasma protein extravasation in the dura induced by both electrical trigeminal stimulation and substance P.[6] This suggests that potent prostaglandin synthesis inhibitors like flurbiprofen may block the vascular inflammation, which forms the final common pathway of migraine, at both the neuronal and blood vessel levels.

Flurbiprofen may be active in migraine prophylaxis through actions at each step of the migraine cascade. It prevents platelet-serotonin release and may alter brain serotonin turnover. It appears to have antinociceptive activity within the brain that may affect trigeminovascular activity. Lastly, it may inhibit the vascular inflammation induced by substance P or trigeminal stimulation.

CONCLUSION

What is the role of flurbiprofen in migraine prophylaxis? The efficacy of flurbiprofen reported in this trial is comparable with that reported in previous studies of propranolol,[37] verapamil,[38] and naproxen sodium.[10,16] The adverse-effects profile was good, showing only the expected problem of gastrointestinal upset in small numbers of patients. Flurbiprofen reduced both migraine duration and intensity. This led to a significant decline in the use of relief medication. Based on this experience, we believe that flurbiprofen can be recommended for use in migraine prophylaxis. If studies with larger numbers of patients and longer duration of therapy verify the efficacy and safety of flurbiprofen, we believe that flurbiprofen may be recommended as a first-line drug for migraine prophylaxis.

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