Montelukast in the Prophylaxis of Migraine: A Potential Role for Leukotriene Modifiers

F. Sheftell, MD; A. Rapoport, MD; R. Weeks, PhD; B. Walker, PA; I. Gammerman, MD; S. Baskin, PhD

Objective.–Clinical observation of a decrease in migraine frequency in patients with comorbid asthma taking montelukast, a specific D4 leukotriene receptor antagonist, or zafirlukast, another leukotriene receptor antagonist, prompted us to explore a possible role for leukotriene modifiers in the treatment of migraine. (A further prompt was a pharmacist colleague’s observation that a number of patients on these agents reported a decreased sensitivity to perfume triggers and improvement in migraine.)

Background.–Nonsteroidal anti-inflammatory agents have been used widely in the treatment of migraine. Another class of anti-inflammatory agents, known as leukotriene modifiers, have not been studied to date with regard to their possible role in the treatment of migraine. The name “leukotriene” is derived both from the parent molecule, which was originally isolated from leukocytes, and from its three double-bond carbon backbone or triene structure. Both prostaglandins and leukotrienes are derived from the metabolism of arachidonic acid, with prostaglandins coming off the cyclooxygenase pathway and leukotrienes derived via the enzyme 5-lipoxygenase. Both prostaglandins and leukotrienes mediate inflammatory responses. The latter have been studied with regard to their role in the pathophysiology of asthma.

Methods.–A prospective, open-label study evaluating the efficacy of montelukast, 10 mg or 20 mg, in the prophylaxis of migraine in 17 patients is presented in this paper. All 17 patients completed the study that consisted of a 2-month baseline run-in period and a 3-month treatment phase.

Results.–Montelukast was extremely well tolerated, and no adverse events were reported by any of the patients. Fifty-three percent showed a reduction of greater than 50% (P < .025) in the frequency of severe attacks, with 41% showing a reduction of greater than 60%. Responders, including modest responders, rated the drug as excellent.

Conclusions.–We conclude, given the limitations of an open-label study design and the small sample size, that montelukast shows potential as an effective, well-tolerated prophylactic agent in migraine. Double-blinded, placebo-controlled studies are warranted. In addition, the leukotrienes, as suggested previously in the literature, may play a role in the pathogenesis of migraine.

Key words: migraine, montelukast, leukotrienes

Abbreviations: LT leukotriene, ETTH episodic tension-type headache, BL baseline

(Headache 2000;40:158-163)

Proinflammatory mediators have been cited widely as playing a role in the pathophysiology of migraine both centrally and peripherally.1-3 Nonsteroidal anti-inflammatory agents and acetylsalicylic acid have been used both abortively and preventively in its treatment.4 In addition, triptans inhibit neurogenic inflammation as a part of their mechanism of action.5 Prostaglandins have been implicated in inflammatory and antiplatelet action, as well as in pain mediation and smooth-muscle contractility.4,5

Prostaglandins, prostacyclins, and thromboxanes are derived from the metabolism of arachidonic acid (Figure 1) via the enzyme cyclooxygenase.5,6 The leukotrienes7,8 (LT), now widely studied in the treatment
of asthma, are also derived from the metabolism of arachidonic acid, but via the enzyme 5-lipoxygenase. Figure 1 shows a simplified overview of the 5-lipoxygenase pathway. Arachidonic acid is split from the cell membrane via an appropriate stimulus and the action of phospholipase A\(_2\). The action of 5-lipoxygenase, requiring the presence of 5-lipoxygenase-activating protein (FLAP), forms LTA\(_4\), an unstable molecule, which is then acted on by LTC\(_4\) synthase to form LTC\(_4\), which is further transformed via other enzymatic steps to LTD\(_4\) and E\(_4\). Leukotrienes C\(_4\), D\(_4\), and E\(_4\) are collectively referred to as the cysteinyl LTs, as each contains a thioether-linked peptide (the amino acid cysteine). Leukotriene B\(_4\) is a proinflammatory mediator as well. A number of actions of the LTs are described below, including their presence in mast cells, which may be of interest to students of migraine and related headache disorders.

Viewing the LT pathways, there are a variety of ways to modify their actions. Three LT modifiers are currently indicated and available for the treatment of asthma in the United States. The first to appear was zileuton, which inhibits the catalytic conversion of 5-lipoxygenase, thus inhibiting the production of the LTs. Zafirlukast appeared next and like montelukast, the most recently introduced, is a specific LTD\(_4\) receptor antagonist. Table 1 summarizes the pharmacokinetic characteristics and mechanisms of the 3 agents.

A review of the literature revealed a number of studies implicating LTs in the pathophysiology of migraine and cluster headache. Some studies have demonstrated elevation of certain of the LTs during migraine and cluster headache, possible action on platelets, as well as a role in the action of feverfew and tolfenamic acid. Moskowitz implicated LTs as one of several possible proinflammatory mediators in migraine. In addition, their action on smooth muscle further attracts our interest as they may be possible vasoactive agents in migraine. Nifedipine and verapamil have been shown to possess anti-LT properties. Based on our clinical observations and the above literature review, we hypothesize that the actions of LTs may have corollaries to a number of current concepts with regard to migraine and that LT antagonists, via a number of potential mechanisms that may be similar to the nonsteroidals, may have applications in the treatment of migraine and related disorders. An open-label study to begin to test the potential clinical efficacy of an LT modifier in migraine is reported here.

**METHODS**

A prospective open-label study was conducted using montelukast, 10 mg every day or 10 mg twice a day, in 17 patients with International Headache Society (IHS) criteria for migraine without aura. Fourteen females and three males, between the ages of 14 and 64 years (mean 45.5 years) were inducted into the study. The mean number of years with migraine was 24.6, with a range of 5 to 54 years. (Table 2 demonstrates the demographics relative to migraine of our study population.) None of the patients had migraine with aura, and most (n = 12) had occasional episodes of episodic tension-type headache (ETTH). Inclusion criteria included the IHS diagnosis of migraine, the ability of patients to differentiate migraine from ETTH, and willingness to keep accurate headache calendars for the 2-month baseline (BL) period and the 3-month open-label treatment phase. Exclusion criteria included patients with chronic tension-type headache, transformed migraine, analgesic/ergot/triptan overuse, and failure on two or more previous trials on preventive agents. No changes in concomitant prophylactic regimens (n = 11) were allowed during the BL period or the active treatment phase.
Detailed headache calendars recording the frequency and intensity of attacks were kept during the BL period and the treatment phase. All patients gave informed consent and were inducted into the study. One of the factors that facilitated induction was the excellent safety profile and tolerability of montelukast. The six patients who were not on prophylactic medication had resisted it due to previous experience with side effects (fatigue, weight gain, cognitive slowing, etc).

Given the relatively short half-life of montelukast (Table 1), patients who typically awoke with attacks were dosed at bedtime. In asthma, this is also the time of dosing for this agent, as the majority of asthma attacks occur during the early morning hours. Interestingly, Solomon found that 80% of the population he studied had onset of migraine 50% or more of the time between 4:00 am and 8:00 am. Patients who told us their attacks typically occurred during the afternoon or evening were dosed accordingly. If no response was seen at a 1-month follow-up, the dose was increased to 10 mg twice a day, or if the response was a decrease of less than a 50% in frequency, patients were offered an increase to twice a day as well.

### Table 1.–LT Antagonist Pharmacokinetic Profiles

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt;</th>
<th>T&lt;sub&gt;max&lt;/sub&gt;</th>
<th>Oral Bioavailability, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zileuton (Zyflo)</td>
<td>5-LOX inhibitor (C4, D4, E4)</td>
<td>2.5 h</td>
<td>1.7 h</td>
<td>Unknown</td>
</tr>
<tr>
<td>Zafirlukast (Accolate)</td>
<td>D4 receptor antagonist</td>
<td>10 h</td>
<td>3 h</td>
<td>Unknown</td>
</tr>
<tr>
<td>Montelukast (Singulair)</td>
<td>D4 receptor antagonist</td>
<td>2.7–5.5 h</td>
<td>3–4 h/2–2.5 h</td>
<td>Tab: 64, Chw: 73</td>
</tr>
</tbody>
</table>

5-LOX indicates 5-lipoxygenase; Tab, tablets; and Chw, chewable form.

The mean number of severe attacks per month at BL was 2.78, with a range of 0 to 4.5. The mean number of moderate attacks per month was 5.5, with a range of 1 to 9. The mean number of mild episodes (ETTH) was 1.53, with a range of 0 to 5. Headache-free days averaged 20.37 per month, with a range of 15 to 24.53.

### RESULTS

Patients were inducted into the study over a period of several months. None of the 17 patients reported any adverse events during the entire 3-month trial. Interestingly, the most common adverse event, by far, reported in clinical trials with montelukast in asthma was headache. The active group (n=1955) reported an 18.4% incidence, with the placebo group reporting an 18.1% incidence of headache. Headache types were not classified. One may speculate here with regard to the question of the natural comorbidity of asthma and primary headache. The incidence of all other adverse events reported in these clinical trials was also comparable for the active group and the placebo group.

Figure 2 shows changes in mean headache attacks per month from BL through the 3-month active period for all intensities of headache. Statistical significance was found for the decrease in severe attacks (P<.025) from 2.78 per month to 1.31. Statistical significance was not observed with regard to changes in moderate attacks, from 5.5 to 4.68, or mild episodes, which showed an increase from 1.53 at BL to 2.02 for the 3-month trial period on the active drug.

Given the small sample size, we constructed scatter plots to show the percent change from BL (active
treatment period/BL-1) for each severity in each patient. Figure 3 demonstrates these changes for the frequency of severe attacks. As stated, there was no increase in the frequency of severe attacks for the 3-month study period. At the extremes, two patients experienced no changes and three had no severe attacks after beginning active treatment. Fifty-three percent showed a decrease of greater than 50% ($P<.025$) in the frequency of severe attacks, with 41% showing a decrease of greater than 60%.

With regard to moderate attacks, no statistical significance was found for the modest decrease in moderate attacks (0.82 per month) (Figure 4). Note, however, that 70.6% showed a decrease in moderate headache, with 29.4% showing an increase in moderate attacks. The possible reasons for the increase in moderate headache will be discussed after reviewing the data for mild episodes.

Figure 5 shows the percent change from BL for mild episodes. Note that five patients were excluded from this analysis secondary to having no mild episodes reported during the 2-month BL evaluation period. Five of the 12 included in the analysis showed an increase in mild episodes, 5 showed a decrease in mild episodes, and 2 showed no change.

Viewing Figures 3, 4, and 5, together we believe that a definite shift from severe to moderate and mild intensities may help to explain why there was no increase in severe episodes and why there was an increase in moderate and mild episodes. Subjective reporting by patients at the end of the active study period was consistent with this explanation.

Four of the 17 patients had their dosage of montelukast increased from 10 mg daily to 10 mg twice a day (2 at 1 month and 2 at 2 months for the remaining month of the study). All 4 experienced a reduction in the frequency of severe attacks for the remaining 1 or 2 months of the study. Given the small sample, no statistical significance is attributed to this reduction. Whereas other patients were eligible for a dosage increase, they declined, citing satisfaction with what appeared to be a modest reduction in severe attacks.

At the end of the 3-month active trial, all patients were asked to rate their satisfaction with montelukast as excellent, good, average, or poor. It was interesting that patients with a reduction of 33% or more in the frequency of severe attacks ($n=13$), rated the drug as excellent. Each of these 13 patients wanted to remain on montelukast therapy, making our request for a reversal phase difficult. Perhaps the fact that montelukast is so well tolerated explains the fact that even those with, what to us, was a modest reduction in headache, rendered a high satisfaction rating.
COMMENTS

While the weaknesses of this study include its open-label design, as pointed out in IHS guidelines, and the small sample size, our results suggest the efficacy of montelukast as a prophylactic agent that is safe and extremely well tolerated in the treatment of migraine. We attempted to add power to the study by having a 2-month prospective BL period, in contrast to IHS guidelines that recommend a 1-month period. We believe that the 3-month active treatment phase is adequate to evaluate potential efficacy. Our primary end point of reduction in the frequency of severe attacks did reach statistical significance, with 53% showing a decrease of more than 50% in severe attack frequency ($P < .025$). We believe that our results suggest that double-blind, placebo-controlled studies are warranted. At the time of writing, two such studies are being planned, one with montelukast and another with zafirlukast at two separate centers. We would recommend that quality-of-life measures and disability instruments be included as additional end points. In addition, given the subjective reports from patients on shortened response time to triptans, the response times to acute therapies should be compared from BL through active treatment.

Previous studies have shown that dosages of montelukast as high as 200 mg are well tolerated, but no further efficacy is shown in asthma beyond the recommended dose of 10 mg daily. However, there are no studies that we are aware of that have investigated the doses required to potentially effect changes in LT activity in the CNS or peripheral vasculature. The results of this open-label clinical trial provide much to speculate about, as do several of the actions of the LTs and their modifiers with regard to an overlap between the pathogenesis and therapy of migraine. In a study by Olness et al., they state: “Mast cells have been implicated in the pathogenesis of migraine because they release many vasoactive substances and nociceptive molecules, such as histamine and nitric oxide.” In another study entitled “Stress-Induced Intracranial Mast Cell Degranulation: a Corticotropin-Releasing Hormone-Mediated Effect” by Theoharides et al., they suggest: “Stress is known to precipitate or worsen a number of disorders such as migraines, in which mast cell are suspected of being involved by releasing vasoactive, nociceptive, and proinflammatory mediators.” We speculate based on our own work that perhaps, as suggested by Moskowitz, LTs may be amongst these mediators. They go on to indicate, “However, no functional association has been demonstrated yet between a migraine trigger and brain mast cell activation.”

Other areas of interest in attempting to elucidate a possible role for the LTs in migraine may include applying LTs to both the trigeminal vascular system model and the calcitonin gene-related peptide model, or both. Are LTs capable of activating these systems and are their modifiers capable of inhibiting their action, or are LTs active in some other area of the migraine cascade? We hope that our work will provoke interest in the exploration of the role of LTs and the modifiers in migraine and related disorders.

From a clinical perspective, if well-controlled studies were to show efficacy for LT modifiers in migraine, they would clearly be the drug of choice for migraine and comorbid asthma. The tolerability of these agents is attractive for use in migraine prophylaxis in adults, as well as children. The chewable preparation of montelukast has a fairly rapid $T_{\text{max}}$ (Table 1), making it a potential candidate for acute therapy or as an adjunct to a triptan. Its minimal p450 interactions may make it a candidate for rational polypharmacy to augment another prophylactic agent.

Are we a side chain or molecule away from developing an effective agent in the treatment of migraine and related headache disorders?
Acknowledgment: Appreciation is expressed to Robert Kevorkian, RPh, for his contribution.

Support Statement: This work was completed without financial support.

REFERENCES