Clinical Pharmacology Update

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Pharmacologic management of migraine—1985[1]

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There are many pharmacologic agents available for treating patients with migraine. One must first decide whether daily prophylactic medication or intermittent acute abortive therapy is indicated. New agents are available for both prophylactic and abortive treatments. Metoclopramide, an antinauseant, has proved to be a useful adjunct in managing acute migrainous attacks. Beta blockers and the new calcium channel antagonists can control the number and severity of attacks in many patients. The anti-inflammatory agents are being used extensively for both migraine and chronic muscle contraction headache. This review focuses on the pharmacologic actions and optimum use of medications in the migraine patient.

Index terms: Clinical pharmacology updates • Migraine, drug therapy

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Migraine, an inherited disorder of vasomotor instability, afflicts, perhaps, 10% to 20% of the population.[1] It can be a disabling condition and not uncommonly causes its victims to be incapacitated for several days with each attack. Recognizing and avoiding provocative factors such as foods, chemical agents, environmental or emotional factors, and physical activities may help decrease the number of attacks. Biofeedback and other nonpharmacologic treatment may also be of help in managing migraine, but the mainstay of therapy for migraine remains the proper use of medications.

When migraine attacks occur more than two or three times a month or are prolonged and unresponsive to acute abortive therapy, prophylactic agents should be considered. Prophylactic medications generally should not be used for persons having headaches less frequently. It is useful to classify the pharmacologic medications as either prophylactic or acute abortive agents.

At this time, there are just three medications that have been approved by the Food and Drug Administration (FDA) as effective agents in the prophylaxis of migraine: methysergide (Sansert), propranolol (Inderal), and nadolol (Corgard). Other beta blockers are effective, and studies with timolol (Blocadren) are awaiting FDA approval. The nonsteroidal anti-inflammatory agents, antidepressants, calcium channel antagonists, alpha stimulators, lithium carbonate, and cyproheptadine may be useful in controlling migraine attacks (*Table 1*). This review will concentrate on new agents useful in the treatment of migraine and on some older agents that are finding new uses in the management of headache.

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Table 1. Prophylactic agents for migraine

Preparation	Daily dose (mg)
Anti-inflammatory agents	
Naproxen (Naprosyn)	500–1,000
Ibuprofen (Motrin, Rufen)	1,200–1,600
Indomethacin (Indocin)	75–200
Antidepressants	
Amitriptyline (Elavil, Endep, and Amtid)	25–100
Phenelzine (Nardil)	45
Doxepin (Sinequan, Adapin)	25–100
Beta blockers	
Propranolol (Inderal)	80–320
Nadolol (Corgard)	40–160
Atenolol (Tenormin)	50–100
Timolol (Blocadren)	20–40
Metoprolol (Lopresor)	100–200
Calcium channel blockers	
Verapamil (Calan, Isoptin)	320–480
Nifedipine (Procardia)	40
Nimodipine	
Flunarizine	
Methysergide (Sansert)	6–8

Methysergide

Methysergide was developed in the 1950s as a prophylactic agent for migraine. It is still one of the most effective agents available if used under proper conditions. It is a derivative of lysergic acid and is chemically related to ergotamine tartrate. Methysergide has several known actions that might account for its effectiveness in controlling migraine and other vascular headaches. Methysergide is a serotonin antagonist, has anti-inflammatory properties, and is a vasoconstrictive agent. It also may affect the hypothalamus and decrease platelet sludging.[2] Studies have shown that methysergide reduces the frequency and severity of migraine attacks in about 70% of patients.[2] This compares well with the figures for propranolol. Methysergide is usually well tolerated. Side effects include gastric irritation, hallucinations, muscle cramps, and induction of fibroproliferative syndromes.

Methysergide has fallen into disfavor because of its rare but definite side effect of inducing fibroproliferative changes with long-term use.[3] Retroperitoneal fibrosis is the most common fibrotic syndrome induced, but pleural fibrosis, endocardial fibrosis, and vascular fibrosis have also been reported. These conditions are reversible upon discontinuation of the drug, but tissue damage can occur if these changes are not recognized early.

This medication should be used only for periods of four to six months followed by a four- to six-week respite. Frequent examinations for the detection of any heart murmurs or bruits over the peripheral vessels are essential. Methysergide is the drug of choice for the treatment of acute episodic cluster headache and can be used intermittently in menstrual migraine or migraine attacks, which tend to occur in a cluster pattern.

Beta blockers

Propranolol was approved as an effective prophylactic agent for common migraine in 1979. It has become the drug of choice for the prevention of migraine because it is effective and well tolerated. Its efficacy compares well to methysergide; good results have been reported in 55%–80% of cases.[4] It, so far, has not been associated with any serious long-term side effects. Several studies show the effectiveness of other beta blockers such as nadolol, timolol, and atenolol.[5–7] Propranolol is lipid soluble and therefore readily crosses the blood-brain barrier.[8] This may account for the sleep disturbances and depression, which, although not common, seem to occur more with propranolol use than with other beta blocking drugs, which are more water soluble.

Propranolol has many effects, several of which may play a role in its effectiveness in migraine[9] (*Table 2*). Propranolol is a competitive antagonist of $beta_1$ and $beta_2$ receptors and hence prevents arterial dilation. The painful phase of migraine is due mostly to the vasodilation of extracranial arteries and to a lesser extent of intracranial arteries. Other mechanisms of propranolol that may be important in controlling migraine attacks include inhibition of catecholamine-induced platelet aggregation, stabilization of membranes, blockage of catecholamine-induced lipolysis, and shifting of the oxygen dissociation curve to enhance oxygen release to tissues.

Serotonin has been postulated to play a role in the vascular changes that take place in the migraine attack and is liberated from platelets during their aggregation. The reduced lipolysis due to propranolol causes decreased formation of arachidonic acid, which is needed for prostaglandin synthesis. Prostaglandins play a role in platelet aggregation and inhibiting their formation thus reduces the amount of platelet aggregation and may reduce serotonin release.

The indications for propranolol (or other beta blockers) are frequent migraine attacks or infrequent but severe attacks that are not well controlled with abortive medications. Contraindications for propranolol include bronchial asthma, heart failure, and heart block. The selective $beta_1$ blockers, atenolol and metoprolol, may at times be used with caution without deleterious effects in persons who have had asthma. Beta blockers should also be used cautiously in diabetics who are taking hypoglycemic agents because the signs and symptoms of hypoglycemia may be altered.

Side effects of the beta blockers are few. Fatigue or tiredness is the most common and occurs in perhaps 10%–15% of persons on these drugs. Diarrhea has occasionally been a problem. Sleep disturbances including nightmares and insomnia are rare symptoms of propranolol use and are even less prevalent with the water-soluble beta blockers. Hypotension, nausea, abdominal pains, and cold extremities are reported side effects of propranolol.[4]

The dosage necessary for control of migraine attacks varies greatly and must be individually titrated. Generally, one begins with a dosage in the range of 80 mg of propranolol a day. I have found propranolol (Inderal-LA) to be well tolerated with good patient compliance since it is used only once daily. Some migraineurs have good control with as low as 40 mg a day, whereas others may need and tolerate 320 mg or more daily. Daily doses of other beta blockers are approximately 80–320 mg of nadolol, 50–100 mg of atenolol, and 100–200 mg of metoprolol. Recently, it has been suggested that continued improvement in migraine control may be evident even after several months of therapy and that control of migraine may be more effective with doses higher than originally suggested.[10]

The duration of propranolol administration varies. After about six months of good control of the migraine attacks, one should attempt to gradually reduce the dosage. Diamond et al[11] have shown that 46% of patients who discontinued the use of propranolol after at least six months of good control had no significant recurrence of attacks during the follow-up period of one to two months.

Alpha receptor stimulators

Clonidine (Catapres) has not been used much in the United States as a migraine prophylactic agent, but has been one of the more widely used agents throughout the rest of the world for controlling migraine.[12–14] Although the beta blockers have largely replaced clonidine, it is still a useful agent at times. Guanabenz (Wytensin) is a similar $alpha_2$ receptor stimulator, which is available in the United States for treatment of hypertension. It was studied clinically as an antimigraine agent in the United States, but was believed to be statistically ineffective and the study was halted. Several patients, however, who had not responded to other agents did well with guanabenz.

These agents diminish sympathetic outflow from the central nervous system by stimulating the inhibitory $alpha_2$ receptors. This action presumably prohibits the initial vasoconstriction, which occurs during the migraine attack. The side effects of these medications are similar with the most common symptoms being drowsiness and dryness of the mouth. The dosage of guanabenz is 4–16 mg twice daily and the dosage of clonidine is 0.1–0.2 mg twice daily.

Table 2. Effects of beta blockers

Blockage of vasodilator receptors
Membrane anesthetic
Anti-anxiety
Blockade of catecholamine-induced platelet aggregation
Decrease platelet adhesiveness
Shifting of Hgb-O_2 dissociation curve
Blockade of catecholamine-induced lipolysis and glycogenolysis

Nonsteroidal anti-inflammatory agents

The number of nonsteroidal anti-inflammatory agents continues to expand as do their uses. Although several have been available for many years, their use both as prophylactic and abortive agents for vascular headache is recent.

Prostaglandin E and prostacyclin have been shown to be potent vasodilators of cerebral vessels and the internal carotid artery.[15–17] They, therefore, may well play a role in the painful dilation phase of migraine. Prostaglandin F_2 is a potent vasoconstrictor of the intracranial vessels.[16,18] Since the aura of migraine is thought to be at least in part due to vasoconstriction, it may be influenced by PGF_{2a}. Thus the anti-inflammatory agents with their antiprostaglandin effects would likely be helpful in both the prophylaxis of vascular headache and the control of acute attacks. Inhibition of prostaglandin synthesis also results in decreased platelet aggregation and, therefore, diminished release of serotonin and possibly other vasoactive substances.

Table 3. Effects of calcium channel blockers

Inhibition of vasoconstriction
Decrease in cerebral hypoxia
Decrease in blood viscosity
Antihistaminic effect

Indomethacin (Indocin) is the treatment of choice for a rare variety of cluster headache called "chronic paroxysmal hemicrania," which was first described by Sjaastad and Dale.[19] Indomethacin also is effective for exertional headaches.[9] I have found it occasionally helpful in the management of cluster headache. Indomethacin has a vasoconstrictive action in addition to its antiprostaglandin effect and occasionally produces a vascular headache probably caused by a rebound vasodilation after the vasoconstriction. Indomethacin has reduced cerebral blood flow and dampened the cerebral vasodilatory response to 5% carbon monoxide.[17]

The dose of indomethacin ranges from 100–150 mg a day in divided doses. I have found naproxen (250–500 mg twice a day) to be an effective prophylactic agent for migraine. Menstrually related migraine may be effectively controlled with intermittent use of a nonsteroidal anti-inflammatory drug beginning just before menses and ceasing at the end of the period.

I have discovered that short-acting nonsteroids such as ibuprofen (Motrin, Rufen) and meclofenamate sodium (Meclomen) are effective as acute abortive drugs at the onset of the migraine attack. Flufenamic acid and tolfenamic acid (not available in the United States), as well as ibuprofen, have been reported to be effective in reducing the duration and intensity of migraine attacks with less side effects than with ergotamine.[20–22] I often use 50–100 mg of meclofenamate sodium, which is rapidly absorbed, at the onset of the migraine with good results. The nonsteroids may also be helpful as an analgesic agent for the control of muscle contraction headache.[23]

Common side effects of the nonsteroidal group include fluid retention, gastrointestinal distress, nausea, diarrhea, and dizziness. Rarely, gastric or duodenal ulcerations may occur. They must be used with caution on a daily basis as a prophylactic agent. Monitoring of renal function must be done, especially in the elderly, since occasionally the nonsteroidal anti-inflammatory drugs cause diminished renal function with subsequent increasing azotemia.

There are currently several studies evaluating the effectiveness of present and new nonsteroidal anti-inflammatory agents in controlling migraine as well as chronic muscle contraction headaches. There are also studies evaluating their use as acute analgesic agents for attacks of migraine and muscle contraction headaches. Undoubtedly, several other agents will be available in the near future and it is hoped that they will be effective, safe agents for controlling headaches and other chronic pain conditions.

Calcium channel blockers

Perhaps the most exciting news recently in the treatment of headaches has been the discovery of the effectiveness of the calcium channel antagonists in controlling both migraine and cluster headaches. Many current studies dealing with these agents are ongoing, but the results of several preliminary reports are promising.[24–28] The action of these agents on the vessels is either that of vasodilation or inhibition of vasoconstriction. Other factors may also play a role in the effectiveness of the agents (*Table 3*).

The specific pathogenesis of migraine and cluster headaches regarding the interplay of neural, hormonal, biochemical, and vascular events is far from being established. However, it is generally agreed that the vascular events are constriction followed by dilation. The calcium channel blockers presumably inhibit the initial vasoconstrictive phase. The calcium ion is necessary for the contraction of vascular smooth muscle cells. This contraction occurs when the intracellular content of free calcium reaches a certain critical level.[29,30] Prohibiting the movement of calcium across the cell membrane thus prevents contraction by keeping the intracellular calcium content below this critical level necessary to induce contraction. Vasoconstriction, whether induced by serotonin, bradykinin, norepinephrine, thromboxane, other prostaglandins, or other vasoconstrictive agents, can presumably be inhibited by the calcium channel blockers.

Verapamil (80 mg four times daily) has been an effective prophylactic agent in migraine and cluster headaches.[26,27] In addition to its antivasoconstrictive and vasodilatory effects, verapamil also inhibits platelet aggregation and serotonin release. Nifedipine seems to be less effective in this regard.[27] Nimodipine, available in the United States only as an experimental drug at this time, seems to be the most effective antimigraine cal-

cium channel blocker, probably because it more selectively acts upon the cerebral vessels.[25,27] Flunarizine has also been reported to be an effective prophylactic agent.[24]

All of the calcium channel blocking agents work slowly and it is thus important to continue them for at least eight weeks. Their effectiveness may increase even after eight to 12 weeks. As a whole, they are well tolerated. Flushing, rash, tachycardia, gastrointestinal disturbances, constipation, fluid retention, and occasional vasodilatory headache have been the most commonly noted side effects. These have rarely been severe enough to warrant discontinuation of the drug.

It is of interest that both amitriptyline and cryprohepatadine, which are useful in the prophylaxis of migraine, are nonspecific calcium channel blockers; this action may be as important as other pharmacological actions accounting for their effectiveness in controlling migraine attacks.[30]

Metoclopramide

Metoclopramide (Reglan), an antinauseant, has become a useful adjunct in the treatment of migraine. Outside of the United States, it has become standard practice to use this agent before using ergotamine tartrate or an analgesic for the acute attack of migraine.

Gastric atony with stasis and distension often occur at the onset of migraine. Studies with effervescent aspirin demonstrated poor absorption during the migraine attack as compared to the interval between attacks.[31] Poor absorption of orally administered analgesics or ergotamine is probably a common situation in the migraine attack. Metoclopramide, unlike other antiemetics, works directly on the gastric wall to promote gastric contraction and gastric emptying. It not only eases nausea and vomiting, but enhances the effectiveness of oral agents.[32,33]

Metoclopramide is generally well tolerated. Occasionally, tremor, shakiness, and nervousness occur. The long-term side effects such as extrapyramidal symptoms are usually of no concern when used intermittently for acute attacks. The dose is usually 20 mg orally at the onset of the migraine attack followed in 15–20 minutes by either an ergotamine preparation, isometheptine, a nonsteroidal anti-inflammatory drug, or other analgesic. Metoclopramide can be repeated in four to six hours if necessary.

Lithium carbonate

Lithium carbonate has been fairly effective in the treatment of cluster headaches. Although originally introduced for the chronic variety of cluster headache, it is effective for the acute episodic variety also.[34] Lithium is also occasionally useful as a prophylaxis of migraine. Its action related to vascular headache is not known, but presumably a central cerebral effect more likely accounts for its effectiveness as opposed to any peripheral action on blood vessel tone, platelets, or the hematopoietic system.[9,35]

The dosage is usually 300 mg three times daily, but occasionally, the total daily dosage may need to be increased to 1,200–1,500 mg. Blood levels should be monitored. Renal and thyroid function must be assessed periodically to evaluate possible long-term toxicity. Common side effects include nausea, weakness, shakiness, nervousness, and drowsiness. These symptoms are much more pronounced with toxic doses. It is most useful in the male patient with cluster headache who has arteriosclerotic disease and/or a history of peptic ulcer disease; in this case, one should avoid using vasoconstrictive drugs or corticosteroids.

Corticosteroids

Corticosteroids in the form of prednisone, triamcinolone, or methylprednisolone have proved to be effective therapy for cluster headache and usually control migraine. The side effects of long-term use limits the practicality of their use in migraine. The few weeks duration of a cluster attack is the ideal situation for their use.

Injection of one of the long-acting steroids, such as methylprednisolone (Depo-Medrol) (40–80 mg) or dexamethasone (Decadron-LA) (8–12 mg, administered intramuscularly), usually brings a prolonged migraine attack under control and may lessen the need for narcotics (Diamond, personal communication, and author's experience). Usually the pain begins to ease in eight to 12 hours. It is my impression that there is a protective effect in that the attacks may not recur as often. Orally, one can use a Medrol dose-pack or Decadron 5–12 pack, which provides a short, decreasing dosage schedule of steroids.

Dihydroergotamine

Good success in managing a group of chronic migraineurs by halting the chronic daily migraine with dihydroergotamine (DHE-45) has been reported (Raskin, personal communication). He

used 1 mg administered intravenously every eight hours for three dosages and this often aborted the headache even though it may have been present chronically for days, weeks, or even months. Many of the patients were able to discontinue daily ergotamine and analgesics. DHE-45 seems to be well tolerated. I believe the greatest advantage of DHE-45 is that it is often effective even after a prolonged period of migraine, whereas ergotamine is usually effective only at the immediate onset of a migraine attack.

Vasodilating agents

The initial vascular event of migraine is vasoconstriction. The painful vasodilation phase may be a compensatory reaction. If vasoconstriction can be alleviated before metabolic or ischemic changes occur, vasodilation may be minimized. In the past, carbon dioxide, amyl nitrate, and other vasodilators were tried at the onset of migraine, but with no consistent benefit.[36] Nitroglycerin used sublingually at the immediate onset of the vasoconstriction has shortened the neurologic or visual aura and prevented subsequent headache about 50% of the time.[37] Only rarely has the headache been aggravated by the use of nitroglycerin when used during the premonitory phase. Isoproterenol by inhalation has also been reported to promptly clear the visual symptoms of migraine.[38] Nitroglyerin, amyl nitrate, or isoproterenol should be tried in patients with severe neurological or visual symptoms with or without headache. These symptoms may be promptly alleviated without exacerbating the vascular headache.

Summary

The physician who attempts to help the patient with migraine has a large variety of pharmacologic agents at his or her disposal. Underlying medical conditions may limit the choice of available agents in any one patient. Many treatment failures result from insufficient levels of the drug being used or not a long enough trial. Most agents do not work within a few days, and indeed, several months of therapeutic dosages may be needed before one can be sure an agent is ineffective. Patients and physicians both tend to become impatient if the situation does not quickly improve and may at times switch to other agents almost on a weekly basis, when all that may be needed is a longer trial or an increase in the dosage.

In the next few years, I anticipate the development of newer and more specific calcium channel blockers and nonsteroidal anti-inflammatory drugs that will be more effective in controlling migraine and cluster headache.

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