

2006 CE Series — Lesson Four

An Update on Migraine Headache and Its Treatment

ACPE Universal Program No. 406-000-06-004-H01

Expiration Date: 3/31/09

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Goals and Objectives

Goals: To provide the pharmacist with information dealing with migraine and its treatment.

Objectives: After completing this article, the pharmacist should be able to:

- a. discuss the pathology of migraine.
- b. list the clinical features of migraine.
- c. describe the therapy for acute attacks of migraine.
- d. discuss the prophylactic treatment of migraine.
- e. counsel patients regarding migraine and its treatment.

Migraine is a symptom complex of periodic headaches, usually temporal and unilateral, often accompanied by irritability, nausea, vomiting, constipation or diarrhea, and photophobia, preceded by constriction of the cranial arteries, usually with resultant prodromal sensory symptoms, and commencing with vasodilation. These characteristics are not necessarily present in each attack or in each patient. Therefore, migraine is a cyclic condition involving an interplay of neural, biochemical, hormonal, and vascular components.

A variety of terms and conditions are classified, at least in part, as migraine. These include classical migraine (headache is preceded or accompanied by transient neurological abnormalities), non-classical or common migraine (not associated with clearly defined neurological disturbance), cluster headache (unilateral intense pain involving an eye and forehead, with flushing and watering of the eyes and nose; attacks last 30-120 minutes and occur in clusters), ophthalmoplegic migraine (migraine-like headache associated with objective evidence of paresis of the extra-ocular muscles), and facial migraine (unilateral facial pain associated with symptoms suggestive of migraine or cluster headache).

The recognition of a variety of disorders that can be labeled as migraine permits greater precision in determining a diagnosis.

Pathology of Migraine

Although it is difficult to ascertain, migraine affects approximately 12% of the population in the United States. A variety of factors appear to contribute to the development of migraine. The condition is frequently familial with a positive family history found in at least 65% of cases. There is a high incidence of migraine in intelligent people and in higher socioeconomic groups and professional occupations. Evidence indicates that ambitious, hard-driving individuals are most subject to migraine, but there is wide variation in the types of personalities encountered.

Migraine frequently begins in childhood or at puberty. Attacks usually decrease in frequency and severity in the late fifties and sixties, which may indicate that cerebral vessels are becoming sclerotic. Onset after the age of 45 is unusual.

Migraine occurs in women approximately two times more often than in men, or women seek treatment more frequently. In women, there is often a relationship between menstrual periods and attacks of migraine.

The exact etiologies of migraine remain unclear. The vascular theory proposes that the headache phase of migraine is a disorder of cerebrovascular regulation. The headache results from vasodilation of blood vessels outside the brain and neurologic symptoms are produced by vasoconstriction of vessels within the brain. The

neural hypothesis is based on changes not associated directly with the major cerebral vessels. This theory proposes that a deficiency in blood volume arises in the occipital lobe of the brain. This precedes the headache by many hours. Then, there is abnormal function of the cerebral cortex which causes the classic aura of migraine. The combined vascular and neural theory proposes that migraine results for abnormal function in the cerebral cortex combined with changes in cerebral vasculature activity. Another theory proposes that serotonin (5-HT) transmission alterations will trigger a migraine attack. During a migraine headache, 5-HT blood levels increase. Other factors that support this theory include drugs that deplete 5-HT may trigger a migraine headache, while drugs used to treat migraine headache have a high affinity for 5-HT receptors.

Many patients develop migraine after the occurrence of frustration, tension, and/or stressful situations. The stress may be insignificant to others and may include exposure to high altitudes and temperature variations, ingestion of certain foods (i.e., those containing monosodium glutamate, tyramine, nitrites), fatigue, mild hypoglycemia, exposure to bright light, and various drugs (reserpine, vasodilators).

An association between migraine and seizures has been suspected, but there is no evidence to indicate a definite relationship. Most patients with migraine have normal EEG's when free of attacks. Those with abnormal EEG's usually do not respond to anticonvulsant drugs as therapy for migraine.

Clinical Features of Classic Migraine

The classic aura of migraine consists of the complaint that approximately 30 minutes prior to the headache the patient develops visual symptoms which impair part of the visual field and have associated photophobia, sometimes with an aversion for a particular color. The visual abnormalities include "seeing stars" and the recognition of various shapes and configurations (i.e., medieval castle battlements). The visual symptoms are at a peak just prior to the headache and then recede. Additional symptoms may include mild hemiparesis and dysphasia.

The headache begins as a dull ache near one side of the forehead and increases in intensity. As the pain increases in intensity, it takes on a pulsating and/or throbbing component and becomes constant. At this stage, the headache often spreads to other parts of the head, the patient becomes nauseated and vomits, and complains of increased photophobia and pain.

The headache often lasts all day, but is terminated by sleep. The frequency of these attacks is variable, but occur less than once a week in 60% of patients, and rarely occur more than three times per week.

General Therapeutic Measures

Accurate diagnosis is essential in the treatment of migraine. Not only must the diagnosis of migraine be made from other causes of headache, but migraine must be distinguished from other forms of headache, such as tension headache.

Patient problems must be determined and evaluated. Although psychological treatment is rarely effective, an understanding attitude is important and frequently insures that a treatment program will be continued long enough to determine its effectiveness.

The initial objective of migraine prevention is the reduction of migraine trigger factors. The various culprits in migraine should be reviewed thoroughly with each patient. In some patients with migraine headaches, modifications of diet and certain habits are the initial approach in patient education that may offer great benefit to the migraine patient.

Many migraine patients have complex environments and require instruction in leisure planning and relaxation techniques. Biofeedback training augments other therapies and can be extremely beneficial to many patients. This therapy uses temperature training (hand-warming) and electromyographic (EMG) feedback techniques to teach patients how voluntarily to control previously unused or involuntary bodily functions. These techniques may offer some benefit to more than half of migraine headache patients.

Although the frequency of attacks may be reduced by the above mentioned measures, the therapy for migraine is basically pharmacologic. Once the diagnosis of migraine is made, a decision must be made regarding the administration of a daily prophylactic agent or only intermittent treatment of the acute attack. In general, individuals with more than two migraine attacks per month should be treated with daily preventive medications, unless there are specific problems precluding this therapy.

Treatment of Acute Attacks

Therapy for acute migraine attacks or abortive therapy is accomplished primarily with the ergot alkaloid derivatives and 5-HT or serotonin receptor agonists.

The 5-HT receptor agonists include sumatriptan, naratriptan, zolmitriptan, almotriptan, frovatriptan, eletriptan, and rizatriptan. Sumatriptan acts selectively at 5-HT receptors in the carotid circulation. Sumatriptan does not cross the blood brain barrier, decrease cerebral blood flow, or have any analgesic effects. Sumatriptan can be administered subcutaneously, orally or as a nasal spray. The usual oral dose is 25 mg, followed by 25 mg to 100 mg after 2 hours, if the migraine headache does not subside. The maximum oral dose in a 24 hour period should not exceed 300 mg. Peak activity after oral dosage occurs, within 2 hours. The subcutaneous dose is autoinjected and is usually 6 mg with a maximum of 12 mg in a 24 hour period. A 2 mg to 3 mg subcutaneous dose has been beneficial in some patients. Peak activity after subcutaneous administration occurs within one hour. Sumatriptan has a half-life of approximately two hours, is metabolized primarily in the liver, and eliminated mainly in the urine. Sumatriptan may cause severe cardiovascular adverse effects rarely, but may cause transient increases in blood pressure, angina, and injection site discomfort.

Zolmitriptan, a selective serotonin receptor agonist that is structurally similar to sumatriptan, is used orally to treat migraine headache. Zolmitriptan is believed to exert its antimigraine effects centrally, since it readily crosses the blood brain barrier. Zolmitriptan reaches peak plasma concentrations in about two hours, is metabolized in the liver, eliminated mainly in the urine, and has a half-life of about three hours. Adverse effects associated with the use of zolmitriptan include paresthesias, warm/cold sensation, and pain and tightness in the chest and neck areas, nausea, dizziness, and somnolence. Drug interactions may occur with ergot, MAOI, cimetidine and oral contraceptives. The initial dose of zolmitriptan is 2.5 mg, while the maximum recommended dose is 10 mg in 24 hours. Zolmitriptan can be administered as a nasal spray or oral or disintegrating tablet.

Rizatriptan is a serotonin agonist used for treatment of migraine headache. It is rapidly absorbed, achieves peak levels in one hour, is metabolized by nonrenal pathways, and has a half-life of about two hours. Rizatriptan must be used with caution in patients with underlying cardiovascular disease. Fatigue, dizziness, pressure in the chest, mild gastrointestinal disorders, and flushing are adverse affects that can occur with rizatriptan. The usual dose is a 5 mg or 10 mg tablet or wafer, which can be repeated in 2 hours. The maximum 24-hour dose is 30 mg. Rizatriptan can be administered as an oral or disintegrating tablet.

Naratriptan is a serotonin agonist used for treatment of migraine headache. It has an onset of about an hour, achieves peak concentrations within 3 hours, is modestly bound to plasma proteins, is metabolized primarily in the liver and has a half-life of about 6 hours. Naratriptan must be used with caution in patients with underlying cardiovascular disease. Fatigue, dizziness, pressure in the chest, mild gastrointestinal disorders, and flushing are adverse affects that can occur with naratriptan. The usual dose of naratriptan 1 to 2.5 mg orally which can be repeated in 4 hours. The maximum 24 hour dose is 5 mg.

Eletriptan is a selective serotonin receptor agonist that is used orally to treat migraine headache in adults. Eletriptan is rapidly absorbed after oral administration, has a bioavailability of about 50 percent, achieves peak plasma concentrations in approximately 1.5 hours, is metabolized primarily in the liver by CYP3A4, and has a half-life of about four hours. Adverse effects associated with the use of eletriptan include dizziness, somnolence, asthania, nausea, paresthesias, and chest symptoms. As with other triptans, eletriptan is contraindicated in patients with ischemic heart disease, peripheral vascular or cerebrovascular disease, uncontrolled hypertension or severe hepatic impairment, and in pregnancy. The usual dose for eletriptan is 20 milligrams to 40 milligrams, which can be repeated after two hours. The maximum dosage is 80 milligrams in 24 hours.

Almotriptan is a selective 5-hydroxytryptamine (5-HT) receptor agonist that is used for the acute treatment of migraine headaches with or without aura in adults. Almotriptan is well absorbed, has an onset of about 30 minutes in most instances, is metabolized primarily in the liver by CYP3A4 and CYP2D6, is eliminated primarily in the urine, and has a half-life of about three hours. Adverse effects associated with the use of almotriptan include nausea, sleepiness, paresthesia, and dry mouth. Since this class of compounds has the potential to cause coronary vasospasm, almotriptan should not be used in patients with ischemic or vasospastic coronary artery disease. Almotriptan should not be used within two weeks of discontinuation of MAOI drugs. The usual dose of almotriptan is 6.25 mg to 12.5 mg orally at the onset of a migraine headache. This may be repeated one time in a 24-hour period after two hours.

Frovatriptan is used for the acute treatment of migraine headache with or without aura in adults. As with other drugs in this group, frovatriptan exerts its effects by binding to and stimulating serotonin. Frovatriptan is similar to the other triptans, but has a half-life of greater than one day. As most migraine headaches usually last from one-half day to several days, the long half-life may be beneficial. Adverse effects associated with the use of frovatriptan include dizziness, fatigue, tingling, dry mouth, hot flashes, chest pain. Individuals with high blood pressure, heart disease, circulation problems and/or history of stroke should not take frovatriptan. The usual oral dose for frovatriptan is 2.5 mg.

The majority of the patients have good relief of migraine headaches with the 5-HT agonists.

Ergot alkaloids have been used to treat migraine for more than fifty years and ergotamine tartrate is the main chemical entity employed. Ergotamine tartrate causes a decrease in the amplitude of pulsations of cranial arteries that parallels its effect on migraine headaches, has prolonged effect, and generally provides consistent relief. To be effective, an adequate dose must be administered as early as possible after the onset of symptoms. Ergotamine can be taken orally, rectally, sublingually, or by inhalation. The oral and rectal forms are available in combination with caffeine, which is added to enhance the effects of the ergot. It is important to use the smallest effective dose by the most effective route as early as possible in an attack. Improper dosage and/or failure to take adequate amounts of ergotamine at the first sign of headache are the most common reasons for failure.

Approximately 65% of the cases respond to ergotamine, but patients vary enormously in their response to the drug. Even in the same individual, alterations in physiologic states may result in various responses at different times. Most patients tolerate ergotamine well, but side effects, such as nausea, vomiting, muscle ache, paresthesias, thrombophlebitis, angina pectoris, and ischemia of the extremities, can occur.

Ergotism is a rare side effect, but drug dependence may occur in those patients who take the drug daily for many years. The drug is contraindicated in peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis, pregnancy, and/or hypersensitivity to this agent. Sedatives and antiemetics (promethazine) may be used to control the nausea and/or vomiting encountered.

Prophylactic Therapy

Prophylactic therapy for migraine is indicated in those patients experiencing more than two migraine attacks monthly, or in those individuals who do not respond to abortive therapy. A variety of drugs, including beta blockers, methysergide, and the tricyclic antidepressants, have been effective for this type of therapy.

Beta-blockers are safe and effective for migraine prophylaxis. There are a variety of mechanisms attributed to their success. These include blocking beta receptors, blocking catecholamine-induced platelet aggregation, decreasing platelet adhesiveness, preventing elevation of coagulation factors during epinephrine release, inhibiting renin secretion, and blocking catecholamine induced lipolysis which results in a decrease in prostaglandins.

Beta-blockers, such as atenolol and propranolol, used in once-daily doses are the drugs of choice for migraine prophylaxis. They are not used in patients with asthma, chronic obstructive lung disease, congestive heart failure, and atrioventricular conduction disturbances. Beta-blockers should not be used concomitantly in diabetic patients treated with insulin or oral hypoglycemic drugs. Beta-blockers are especially helpful for patients with migraine

and severe hypertension, angina pectoris, or thyrotoxicosis, in whom ergot preparations are contraindicated. In these situations beta-blockers are useful in the treatment of headache and the concomitant disorder.

Calcium channel blocking drugs, such as verapamil, have been effective in migraine prophylaxis and produce minimal adverse effects. A critical concentration of intracellular calcium is necessary for contraction of vascular smooth muscle cells. Consequently, the blocking of calcium movement across the cell membrane should reduce the vasoconstriction which occurs as part of the migraine attack. This is a postulated mechanism of action, although other effects may be associated with the antimigraine activity of these drugs. The full therapeutic effect of calcium channel blockers may not be achieved for one to two months. Constipation and fluid retention are adverse effects.

The tricyclic antidepressant drugs, particularly amitriptyline, have been used effectively in migraine prophylaxis. The antimigraine effects are not related to their antidepressant activity, although this may be important in some instances. The adverse effects encountered with tricyclic antidepressants for this indication are primarily the anticholinergic type, such as constipation. Patients who do not benefit from these drugs may have positive results with phenelzine, a monoamine oxidase inhibitor which has been useful in prophylactic therapy of migraine.

A very effective drug for prophylaxis is methysergide, a peripheral serotonin antagonist and central serotonin agonist that causes a stimulation of serotonin activity at receptor sites. It is effective in a majority of patients, but there are many potential side effects, some of them serious, that may be encountered. These include abdominal discomfort, muscle cramps, paresthesias, edema, and depression which can occur during the early stages of therapy, while cardiac fibrosis and retroperitoneal fibrosis are serious long-term side effects.

The dose of methysergide should increase gradually over a 1-2 week period from an initial test dose of one milligram to a total of two milligrams three times each day. Since the long-term side effects are very serious, the drug should not be used for longer than six months, followed by two months off before treatment is resumed. Methysergide should be used after other compounds with fewer side effects are shown not to be effective. Contraindications are similar to those for ergotamine.

Valproate is an antiepileptic drug that has been used to prevent migraine headaches. The usual maintenance dose after titration is one to two grams a day. Valproate is usually well tolerated.

Indomethacin may be useful in preventing certain types of migraine headaches (e.g., exercise induced). In addition, indomethacin has been used to treat "migraine-like" syndromes which typically include pain associated with neck injuries. Doses used vary, but is usually 100 mg to 200 mg a day for 2 or 3 days to obtain relief.

Other Migraine Therapy

The majority of females with migraine complain that most migraine attacks are associated with their menstrual period. Nonsteroid anti-inflammatory drugs, such as fenoprofen and naproxen, have been effective, particularly when administered several days before the onset of menses and throughout the menstrual period.

Status migraine are attacks which fail to resolve in 24 to 36 hours. The use of corticosteroids, such as dexamethasone, may be effective.

Conclusion

Migraine headache is a significant problem that affects many people. Patients with migraine should be evaluated by an experienced specialist. Once the appropriate therapy is determined, patients should be counseled that compliance is essential to improvement and/or control of the problem.

Table 1
Major Drugs Used To Treat Migraine

Generic Name	Example Of Brand Name
Ergotamine	Ergomar
Ergotamine/caffeine	Cafergot
Methysergide	Sansert

Dihydroergotamine	DHE 45
Sumatriptan	Imitrex
Propranolol	Inderal
Atenolol	Tenormin
Amitriptyline	Elavil
Verapamil	Calan
Fenoprofen	Nalfon
Naproxen	Naprosyn
Dexamethasone	Hexadrol
Promethazine	Phenergan
Valproate	Depakote
Indomethacin	Indocin
Zolmitriptan	Zomig
Naratriptan	Amerge
Rizatriptan	Maxalt
Almotriptan	Axert
Frovatriptan	Frova
Eletriptan	Relpax

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