Acute Management of Migraine

Debashish Chowdhury

Abstract
Migraine is a brain disease whose principal symptom is episodic intense throbbing pain in the head which is often accompanied by photophobia, phonophobia, nausea and vomiting. Primary objectives of migraine treatment are to abort the acute attacks, treat associated symptoms and prevent future attacks. With a majority of migraine patients being young, they will need a treatment plan to suit their professional work, leisure and reproductive concerns. Non specific anti-migraine drugs like non-steroidal anti-inflammatory drugs, anti-emetics, narcotics, and sympathomimetics are usually helpful in mild to moderate attacks. Specific drugs like triptans and ergots are useful for moderate to severe attacks. In step care approach, the patients are started with the simplest options like simple analgesics first followed by non-steroidal agents, then ergot preparations and eventually triptans if they do not respond. In stratified care approach, the attacks and the patients are stratified according to the severity and therapeutic response. Those with severe disabling episodes are given specific anti-migraine medications like triptans whereas patients with mild or low disability are treated with simple analgesics. Currently, the most favored acute anti-migraine medication is a triptan. At marketed doses all triptans are effective as compared to placebos and generally well tolerated. Amongst them however, rizatriptan 10 mg, eletriptan 80 mg and almotriptan 12.5 mg provide the highest likelihood of consistent success. Triptan related adverse events are usually short lived, mild and clinically insignificant. Ergots are slowly being replaced by triptans. This is because of their adverse side-effects, low bioavailability and high potential for abuse that can lead to overuse headache.

Introduction
Migraine is now well-established as a brain disorder. The main symptom of migraine is throbbing pain in the head. Characteristically the headache is hemicranial although bilateral headache is not uncommon. Migraine headaches are often accompanied by other dysfunctions like photophobia (hypersensitivity to light), phonophobia (hypersensitivity to sound), nausea and vomiting. There is great variation in symptoms from patient to patient and from attack to attack in the same patient. The primary objectives of acute migraine treatment will therefore be to abort the acute attacks, treat associated symptoms and prevent future attacks.

Migraine attacks essentially include four phases.¹ The first phase is that of the Prodrome which precedes the headache by hours to days and consists of altered mood, irritability, depression or euphoria, fatigue, yawning, excessive sleepiness, craving for certain food (e.g., chocolate), stiff muscles (especially in the neck), constipation or diarrhea, increased urination etc. The second phase is that of the Aura. It is a short-lasting brain dysfunction which usually precedes the headache. Visual aura is the most common type seen in migraine. Classically the patient develops a visual disturbance in the form of flashes of black & white or multicolored zigzag lines. These develop and expand slowly over 5 to 20 minutes and usually last for less than 60 minutes. Sometimes other forms of aura are reported such as sensory symptoms (like auditory or olfactory hallucinations, tingling, pins and needle sensations in arms and legs and face etc), language symptoms (difficulty in speaking, finding words, naming etc) and motor symptoms (like weakness of limbs etc). The aura is often followed by intense Headache which lasts from 4 hours up to 3 days. This constitutes the third phase. The headache usually builds up in severity over time and intensifies on activity. An abnormal sensitivity to pain develops in many patients where even an innocuous stimulus like combing hair is perceived as painful (this is called “allodynia”). The fourth phase is that of Postdrome when even though the patient recovers from headache, general malaise and exhaustion persist for variable period of time. Not all these phases are always present in all patients and in all attacks of migraine. Treatment paradigms in migraine should also include treatment of these “phases”

Pathophysiology Relevant to Acute Treatment
Migraine was initially considered a vascular headache implying thereby that the pain occurs primarily due to abnormal dilatation of blood vessels of the face and brain. This hypothesis has now been largely discarded. Currently, it is thought to be primarily a disease of brain in which a spreading electrical change in the brain (called the cortical spreading depression, CSD) leads to release of inflammatory mediators (called neurogenic inflammation). CSD is now considered to also be the mechanism responsible for migraine aura. Neurogenic inflammatory mediators activate the trigeminal nerve, the main sensory nerve supplying the head and face. It is possible that vascular and myofascial nociceptive inputs also contribute. The nociceptive inputs are strongly modulated in the nucleus caudalis which then project the net facilitatory and inhibitory responses to the thalamus and then to cortex for the pain perception to occur.² Central sensitization of these neurons is thought to be responsible for allodynia which occurs within 40-60 minutes. Hence, it is important to start the triptans before the development of central sensitization.³ From the neuro-biochemical point of view, the serotonergic system is implicated for the genesis of pain. Serotonin is an important neurotransmitter. Specific anti-migraine drugs depend on the serotonin receptors for their action (see below). It is important to understand these basic facts about the pathogenesis of migraine headaches in order to be able to treat the patients effectively.

General Principles of Acute Migraine Management
The general principles of acute migraine therapy have been tabulated in (Table 1). They are briefly outlined here:

1. Establishing the correct diagnosis
Migraine is still essentially a clinical diagnosis. Detailed history taking is therefore mandatory. In a typical situation

*Professor of Neurology, G.B.Pant Hospital, New Delhi, India*
features such as episodic headaches lasting for hours, hemicranial distribution, throbbing or pulsatile character, presence of aura and other accompaniments like nausea, vomiting, photophobia and phonophobia, relief with sleep and aggravation by routine physical activity, leave little room for doubt regarding the diagnosis. When the history is less typical, when the subject is seen with or shortly after the first headache or when there are abnormal findings on neurological examination, imaging studies like CT scan or MRI may be needed to exclude structural abnormalities mimicking migraine. It is also important to understand that migraine headaches may coexist with other headaches. It is mandatory to enquire, inform and educate the patients regarding the different types of headaches because treatments will vary.

2. Use of headache diaries
The headache diary is an important tool to objectively record the frequency, severity, duration, associated symptoms, and medication intake by the patient. For measuring severity and disability, validated scales are available which can be easily used by the patients. Examples include MIDAS and HIT scores. They may clearly indicate that medication overuse headache has evolved due to ergot or triptan overuse.

3. Educating the Patient
For migraine treatment to succeed, we need to explain the disease and develop a good rapport with the patient. Physicians should assess the need of a particular drug based on headache characteristics and also age, sex, occupation, impact of potential or actual disability, individual contraindications and patient preferences. It is important to emphasize that acute treatment of migraine is not just about prescribing a drug but also about making the patient understand the disease.

4. Avoidance of Triggers
Hormone related fluctuations are well-known triggers for menstrual migraine. There are also other common triggers for migraine. It is good practice to give the patient list of the common triggers (Table 2). Patients should be encouraged to adopt a healthy lifestyle by regular eating, sleeping and daily exercises and although these measures may appear quite simple, they may be quite rewarding. Triggers may be related to local socio-cultural practices. For example, migraine triggered by “head bath” or “hair washes” in Indian females and “Yom- Kippur” and “First of Ramadan” headaches seen during religious fasting in Jews and Muslims.5,6

5. Setting the right Goals
The ideal acute drug should be able to make the patient pain-free within the shortest possible time without producing any significant adverse effects. The drug should be able to take care of the disability as well as impaired social functioning. Acute attacks of migraine vary considerably between and within the subjects in terms of severity, associated symptoms, disability and social impact. Therefore treatment must be tailored to individual needs of the patient.

6. Treatment of associated symptoms
Nausea, vomiting and photophobia are troublesome associated symptoms of migraine. Anti-emetic and prokinetic drugs are useful for nausea and vomiting. Early treatment with triptans also relieves nausea, vomiting and photophobia.

7. Optimizing treatment
Taking medication too late in the attack and suboptimal doses are the common reasons for poor response. Prior experience with efficacy or adverse drug effects should be enquired into. The appropriate route of drug administration may also determine the outcome. For example, if vomiting is the main symptom, oral administration of a drug may not produce good results. Rectal, intranasal or subcutaneous injections may be preferable. It is also useful to know about the contraindications when using a particular agent. For example, history of coronary artery disease, cerebral vascular disease, uncontrolled hypertension and pregnancy contraindicates ergots and triptan use. Similarly aspirin and NSAIDS are contraindicated in active gastric ulcers and bleeding disorder patients. In patients with moderate to severe attacks, combination therapy of NSAIDS with triptans may be considered. Similarly combination of aspirin or other NSAIDS with metoclopramide or domperidone is worthwhile in patients with nausea and vomiting.
8. Rescue treatment

This should be discussed with the patient during routine evaluation. Several agents are available for this purpose including opioids and corticosteroids. If rescue medications are required more than 2 times a month, the abortive treatment strategy should be reviewed and need for preventive therapy reassessed.

9. Nonpharmacologic treatment strategies

Patients with significant psychiatric comorbidities like depression and anxiety, those with coping problems and stress disorders need psychotherapy and psychiatric counseling along with pharmacologic therapy. These should be instituted along with acute treatment plan simultaneously.

Treatment Approaches

There are in general, two treatment approaches for acute migraine headaches.

A. Step care approach

In this approach, the patients are started with the simplest options like simple analgesics. If they do not respond, ergot preparations and eventually triptans are added. This is a cost-effective methodology. However, much time may be lost and successful and optimum treatment may be delayed in many patients.

B. Stratified care approach

In this approach, the attacks and the patients are stratified according to the severity and therapeutic response. Those with severe disabling episodes are given specific anti-migraine medications like triptans whereas patients with mild or low disability are treated with simple analgesics. In clinical practice however, both these approaches may be combined.

Drug Treatment of the Acute Attack

Drugs that are used in acute migraine attacks can be grouped into two broad types: specific and non-specific. The specific group includes ergot alkaloids and triptans while the latter group includes anti-emetics, non-steroidal anti-inflammatory drugs, narcotics, sympathomimetics and other miscellaneous agents.

A. Non-specific Drugs

1. Non-steroidal anti-inflammatory drugs

These are most widely used drugs for the acute treatment of migraine. However, many patients use them either with inadequate doses or quite late during the headache without deriving much benefit.

Mechanism of action

NSAIDS possess anti-inflammatory, analgesic and antipyretic properties. NSAIDS exerts their effect in migraine by inhibiting prostaglandins and prolongation of serotonin turnover in brain neurons. To treat acute migraine attacks, the trick is to give an agent which can be readily absorbed within a short time: aspirin with tmax of less than half an hour and naproxen sodium with tmax upto 1 hour are good choices.

2. Combination analgesics:

Many analgesics especially aspirin and acetaminophen are combined with caffeine, barbiturates or opioids to increase their effectiveness. Such combinations should generally be avoided. Treatment should be started as early as possible and preferably in the highest dose that a patient can tolerate. NSAIDs are also useful choices in patients who cannot receive ergots or triptans because of cardiovascular or other contraindications. COX 2 inhibitors may be the choice in patients who are more prone to gastrointestinal irritation from conventional NSAIDs. Parenteral NSAIDs like diclofenac or ketorolac may be useful in the emergency room. The dosing of various NSAIDs available for migraine is tabulated below.

3. Antiemetics

Antiemetics such as metoclopramide or domperidone administered prior to NSAIDs intake improves oral absorption and ameliorates the gastrointestinal manifestations of migraine.

4. Opiate Analgesics

Oral opiate combinations may occasionally be considered for use in acute migraine when sedation side effects will not put the patient at risk and/or the risk for abuse has been addressed.

5. Miscellaneous agents

Intranasal lidocaine (4% solution) and intravenous magnesium sulphate (1 gm and 2 gm) have been tried in acute migraine attacks in emergency room with inconclusive results. Steroids have been found to be useful in status migrainosus anecdotally in open labeled trials (see below).

B. Specific anti-migraine drugs

1. Ergot alkaloids

Ergot alkaloids have been used in the treatment of migraine since 1926. These compounds are potent vasoconstrictors which is probably their principle pharmacologic effect on migraine pain. Unlike triptans, they act on a wide range of receptors including 5HT1A, 5HT1D, 5HT2, D2 and alpha and beta adrenoceptor. The ergot alkaloids which are used in the treatment of migraine are ergotamine and dihydroergotamine(DHE). Although these agents have been used extensively for the last 75-80 years, they are slowly being replaced by triptans. This is because of their adverse side-effects, low bioavailability (unpredictable pharmacokinetics) and high potential for abuse. Nausea (10-20%) is its most limiting side-effect. As persistent vasoconstriction occurs after a single therapeutic dose of ergotamine, it should not be given daily. This may lead to chronic vasoconstriction and habituation. Patients should not be allowed more than two doses per week. DHE also has a low oral bioavailability. However, after intravenous injection DHE is distributed quickly.

Common side-effects include nausea, vomiting, abdominal discomfort, acroparesthesia and leg cramps. Coronary and cerebral vasospasm and vasoconstriction can be caused by ergotamine. Anorectal ulcers can be seen both after chronic oral and single rectal use. Fibrosing disorders involving pleura, pericardium, heart valves, retroperitoneum and peripheral neuropathy have been reported after chronic use of ergotamine. With parenteral DHE, the most common side-effect is nausea. With intranasal DHE, transient nasal congestion, nausea and throat
Triptans may produce adverse events. However in the side-effects it is postulated that triptans abort migraine attacks by their central counterparts. Based on numerous biochemical and pharmacological studies in migraine patients, it was long speculated that compounds mimicking 5-HT at the carotid vascular receptors might abort migraine attacks. Tryptamine derivatives (triptans) were therefore synthesized to achieve selectivity at the carotid vascular 5-HT 1B/1D receptors. The first compound developed was called sumatriptan. However, soon it was found that sumatriptan has certain limitations, namely, low oral bioavailability, high headache recurrence because of short half live and contraindications in patients with coronary artery disease. Hence, newer 5-HT 1B/1D receptors agonists were developed and together as a group these are called triptans. Currently, six other triptans namely the zolmitriptan, rizatriptan, naratriptan, eletriptan, almotriptan, and frovatriptan are available for clinical use. Since their introduction in 1991, triptans have revolutionized acute migraine treatment.

Mechanism of action
It is postulated that triptans abort migraine attacks by multiple mechanisms. The proposed mechanisms are direct contraction of dilated extra cranial cerebral blood vessels, suppression of neuropeptide (like calcitonin gene related peptide) release from peripheral nerve endings around blood vessels, inhibition of impulse transmission centrally in the trigeminal nucleus caudalis, and presynaptic blockade of synaptic transmission between axon terminals of the peripheral trigeminovascular neurons and cell bodies of their central counterparts.

Side-effects
Triptans may produce adverse events. However in the majority of patients, these are short lived, mild and clinically insignificant. The various side-effects known as triptan symptoms include tingling, numbness, a warm sensation, heaviness, and pressure tightness in different parts of the body including the chest and neck. Additionally, dizziness and sedation may occur and patients should be warned about driving or performing complicated task for at least one hour after administration. Reports of coronary spasm resulting in angina and myocardial infarction have appeared from time to time after sumatriptan intake. However, it is generally held that fatal cardiovascular events are remarkably rare. These complaints are more common with subcutaneous injections compared to oral tablets.

Drug interactions
For patients taking propranolol as a prophylactic treatment for migraine, the dose of rizatriptan should be reduced to 5 mg as the level of rizatriptan is almost doubled by propranolol. Simultaneous use of ergot derivatives with triptans is contraindicated.

Choosing a Triptan
a. Based on onset of action
Subcutaneous sumatriptan has onset of action within 10 minutes; intranasal sumatriptan and oral rizatriptan has on onset of action after 15 minutes; oral sumatriptan 50-100 mg has onset of action after 30 minutes; rectal sumatriptan after 30 to 60 minutes; naratriptan after 60 minutes. In this context therefore, the information regarding the time for the headache intensity to peak becomes crucial and the agent is chosen accordingly.

b. Based on associated symptoms
If significant nausea and vomiting is present, oral administration of triptans may not be feasible. Subcutaneous sumatriptan is probably the best alternative followed by intranasal or rectal administration formulations.

c. Based on recurrence of headache
In clinical practice, about 40% of patients treated with sumatriptan have recurrences. Therefore, in patients with headache recurrence either the second dose of triptan can be repeated or naratriptan or frovatriptan may be worth trying. If multiple recurrences occur, then probably drugs other than triptans should be used. A patient failing to respond to a particular triptan may respond to another triptan.

Special situations
1. Treatment of acute migraine attacks in children
Principles of migraine treatment remain the same in children. In children under 15 years, acetaminophen (15mg/kg; maximum 1 gm) and ibuprofen (10mg/kg) have been found to be effective and safe. Aspirin is prohibited in migraine patients less than 15 years because of its association with Reyes syndrome. Data on other NSAIDs and other non specific drugs are non existent.

2. Menstrual migraine
For most of the patients having menstrual attacks of migraine, the acute therapy remains the same. The drugs are given 2-3 days prior to the expected menstruation and continued upto 2-3 to 7 days during menstruation. These include NSAIDs, estrogen supplements, triptans (naratriptan and frovatriptan) and magnesium.

3. Acute treatment during pregnancy and lactation
Pre-existing migraines usually show an ameliorating trend during pregnancy. New onset migraine during pregnancy pose a diagnostic challenge and all symptomatic causes should be ruled out. Principles of acute treatment of migraine remain the same in pregnant women. Mild to moderate attacks may be treated with rest, relaxation strategies and other non-pharmacological means. In non-responders and those with severe attacks, non specific medications can be tried. Drugs with longer record of use in pain treatment should preferably be used. These include opioid analgesics, acetaminophen, NSAIDs, metoclopramide and phenothiazines.
4. Special types of migraine

a. Hemiplegic migraine

Hemiplegic migraine (HM) may occur in familial or sporadic form. Since the condition is rare, only anecdotal and open labeled studies of acute treatment are available. Intranasal ketamine has been found to reduce the severity and duration of neurologic symptoms in 5 out of 11 patients. Other drugs reported to be successful with dramatic results are intravenous naloxone (0.4 mg) and intravenous verapamil. Ergotamine and DHE although appeared safe in some reports, should generally be avoided. Triptans have been used in few cases without detriment.

b. Basilar Migraine

Basilar migraine is characterized by posterior fossa/brain stem symptoms which are bilateral in nature. All types of auras can occur except motor aura. NSAIDs are the mainstay of acute treatment.

c. Status migrainosus

Patients of migraine without aura sometimes have severe headache lasting for more than 72 hours. This is known as status migrainosus. Treatment includes aborting the headache, management of the nausea and vomiting, correction of metabolic abnormalities if any and treating psychiatric aspects like mood disorders. Drugs such as intravenous DHE, intravenous sodium valproate, intravenous droperidol, intravenous lidocaine, intravenous corticosteroids and other dopamine antagonists have been used to treat this condition.

Conclusion

It is evident from the foregoing discussion that acute treatment of migraine has much to offer to the patients at the present time. Treatment has to be tailored to individual needs and individual attacks. Patient participation in the decision making process in terms of prioritizing their needs is the key to the success of acute migraine therapy. However, despite the availability and evidence of efficacy of migraine specific drugs, only a minority of patients use them. This should be a wake-up call for all of us.

References

5. Ravishankar K. ‘Hair wash’ or ‘head bath’ triggering migraine – observations in 94 Indian patient. Cephalalgia 2006; 26: 1330-1334