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AN OVERVIEW ON MIGRAINEOUS HEADACHE AND IT'S PREVENTIVE MEASURES

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ABSTRACT

The most common type of vascular headache is migraine. Migraine headaches are usually characterized by severe pain on one or both sides of the head, an upset stomach, and, at times, disturbed vision. Women are more likely than men to have migraine headaches. When headaches occur three or more times a month, preventive treatment is usually recommended. Drug therapy, biofeedback training, stress reduction, and elimination of certain foods from the diet are the most common methods of preventing and controlling migraine and other vascular headaches. One of the most commonly used drug for the relief of migraine symptoms is Sumatriptan. Other drugs used to prevent migraine include methysergide maleate, which counteracts blood vessel constriction; propranolol hydrochloride, which reduces the frequency and severity of migraine headaches; ergotamine tartrate, a vasoconstrictor that helps counteract the painful dilation stage of the headache; amitriptyline, an antidepressant; valproic acid, an anticonvulsant; and verapamil, a calcium channel blocker. The paper shows that, at present, migraine attacks are managed with pain-killers, herbal medications, and alternative therapies. But research continues to discover more effective, safer and readily available modes to control migraines.

KEY WORDS

Vascular headaches, Vasoconstrictor, Sumatriptan, Ergotamine Tartrate

INTRODUCTION[1]

According to World Federation of Neurology "Migraine is a familial disorder characterized by recurrent attacks of headache widely variable in intensity, frequency and duration. Attacks are commonly unilateral and are usually associated with anorexia, nausea and vomiting" The proportion of the population who experiences regular headaches is surprisingly large, with about 70%of people reporting one or more headaches per month. World 15-20% of women and 10-15% of men suffer from migraine. In India, 15-20% of people suffer from migraine.

Migraine greatly affects quality of life. The WHO ranks migraine among the world's most disabling medical illnesses.

Many healthcare professionals other than physicians may be contacted by headache sufferers for care, including:

1. Pharmacist: for general advice and over the counter medication,
2. Optician: for headache related to eye strain,
3. Dentist: for headache associated with jaw and face,
4. Practice nurses: at the various clinics that they run,
5. School nurses: for headache in children, and
6. Chiropractors and other alternative healthcare providers.

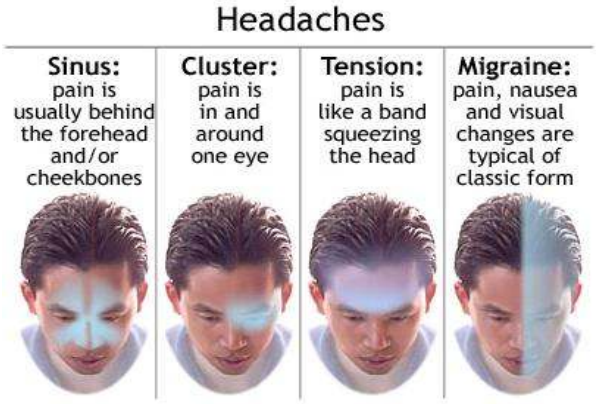

Figure 1
***Types of headaches*[2]**

***Phases of Acute Migraine*[1]**

1. Prodrome
2. Aura
3. Headache
4. Postdrome

Migrainous headache is most frequently seen disabling in primary care. It is clinical syndrome consisting of attacks of multiple symptoms, which occur in an episodic fasion over decades of a sufferer's life, attacks being separated by symptom-free intervals. These include[2, 3]:

1. Headache
2. Nausea
3. Sensory sensitivity
4. Muscle pain
5. Cognitive disruption
6. Autonomic symptom

Factors responsible for Migraine Trigger:

1. Food
2. Disturbed sleep pattern
3. Hormonal changes
4. Drugs
5. Physical exertion
6. Visual stimuli
7. Auditory stimuli
8. Olfactory stimuli
9. Weather changes
10. Hunger
11. Psychological factors

The two subtypes of Migraine with aura and without aura differ only in presence of phase of reversible sensory symptom in usually 1 hour preceding the development of headache. Attack of Migraine without aura equally and even more severe than with aura[4].

Aura is a warning or signal before onset of headache

Symptoms:

1. Flashing of lights
2. Zig-zag lines
3. Difficulty in focussing

Duration: 15-30 min

CLINICAL FEATURES[5]

5-HT$_{1B/1D}$ AGONIST[15, 16, 17]

5-hydroxytryptamine$_{1B/1D}$-receptor agonists, or triptans, are the most recently introduced class. Each of the 4 available triptans (sumatriptan, zolmitriptan, naratriptan, and rizatriptan) is effective in ending a migraine attack, but comparative trials have shown differences between individual drugs in the time to pain relief and the percentage of patients who obtain pain relief.

Medications to prevent or reduce the frequency of migraine tend to be less specific and effective than medications for the acute treatment of migraine. As a class, triptans are generally well tolerated and may be considered drugs of choice for the acute treatment of moderate to severe migraine.

***Proposed biphasic mechanism of action of triptans on meningeal nociceptors during migraine**:*

Step I: soon after systemic administration, triptan molecules bind to 5HT receptors on the dural branch of the meningeal nociceptor and activate them. This initial action of the drug exacerbates, rather than alleviates the patient's perception of pain.

Step II: about 20 min after administration, triptan molecules eventually cross the blood–brain-barrier and bind to presynaptic 5HT1B1D receptors on the central branch of the meningeal nociceptor in the dorsal horn. As they activate these receptors, they effectively block synaptic transmission between the nociceptor and the central neuron in the dorsal horn. As long as the central neuron is not sensitized, that is, as long as its firing remains dependent on incoming impulses from the meninges, triptan inhibition of synaptic transmission in the dorsal horn renders the central neuron quiescent and eliminates migraine pain.

Alpha-2 agonists

Alpha-2 agonists are minimally, and not conclusively, efficacious anticonvulsants. Evidence for efficacy of the other anticonvulsants was weaker. The only placebo controlled trial of carbamazepine suggested a significant benefit, but this trial was inadequately described in several important respects.

Antidepressants

Amitriptyline has been more frequently studied than the other agents, and is the only antidepressant with fairly consistent support for efficacy in migraine prevention. Anticholinergic symptoms were frequently reported with the tricyclic antidepressants studied, including amitriptyline. Adverse events were less common with selective serotonin reuptake inhibitors, with nausea and sexual dysfunction being the most frequently observed symptoms.

Beta-blockers[12]

The *AHCPR Technical Review* analyzed 74 controlled trials of beta-blockers for migraine prevention, Evidence consistently showed the efficacy of propranolol in a daily dose of 120 mg to 240 mg for the prevention of migraine. Three studies comparing daily propranolol doses of 80 mg and 160 mg reported mixed results. One trial comparing propranolol and amitriptyline suggested that propranolol is more efficacious in patients with migraine alone; amitriptyline was superior for patients with mixed migraine and tension-type headache. Metoprolol is efficacious for the prevention of migraine. Timolol, atenolol, and nadolo are also likely to be beneficial based on comparisons with placebo or with propranolol. Adverse events most commonly reported with beta-blockers were fatigue, depression, nausea, dizziness, and insomnia.

One trial each showed cyclandelate to be less effective than flunarizine more effective than pizotifen and not significantly different from propranolol. Two trials of verapamil and one of nifedipine reported high dropout rates due to adverse events.

NSAIDs

A meta-analysis of five of seven placebocontrolled trials of naproxen or naproxen sodium suggested a modest, but statistically significant, effect on headache index or frequency. Similar trends were observed in placebo-controlled trials of flurbiprofen, indobufen, ketoprofen, lornoxicam, mefenamic acid and tolfenamic acid.

Serotonergic agents

1. ***Ergot derivatives*** – In contrast, TR-DHE was significantly better than amitriptyline at reducing the number of hours of extremely severe and severe migraine-like pain.

2. ***Methysergide -*** It is a semi-synthetic ergot alkaloid that is structurally relatedto methylergonovine. It was one of the first pharmacological agents to be used and studied for theprevention of migraine, but its usefulness is now limited by reports of retroperitoneal and retropleural fibrosis associated with long-term, mostly uninterrupted, administration. Thirteen controlled trials examined the efficacy of ergot derivative compounds for the prevention of migraine. TR-DHE, in a daily dose of 10 mg, had the strongest support, with consistently positive findings in four placebo-controlled trials. Fourplacebo-controlled trials suggested that methysergide was significantly better than placebo at reducing headache frequency. Adverse events were no more common with methysergide than with pizotifen.

Other Treatments[18]

Hormone Therapy –Two placebo-controlled trials of estradiol used perimenstrually in a gel or patch form suggested that a relatively high dose of this hormone (1.5 mg per day [gel]) may be efficacious in women whose migraine headaches are closely associated with the menstrual cycle.

The evidence does not support the efficacy of estradiol or flumedroxone in women whose migraines are not associated with their menstrual cycle or in men who have migraine.
Adverse events associated with estradiol were minimal and caused very few withdrawals.
Adverse events were much more common with flumedroxone than with placebo or methysergide.

Riboflavin – One trial compared a high dose of vitamin B_2 (400 mg) against placebo. A significant benefit was observed three and four months following initiation of treatment.

Feverfew – Two trials, distinctly different in design, compared the herbal remedy, feverfew, with placebo or no treatment. One trial was conducted in a self-selected group of feverfew users and showed that withdrawal of feverfew led to a statistically significant increase in headache frequency.
Consideration of nonpharmacological therapies are reviewed in the Evidenced-Based Guidelines for Migraine Headache: Behavioral and Physical Treatments.

Cautions for medication use

A. Initiate therapy with the lowest effective dose. Begin with a low dose of the chosen pharmacological agent and increase the dose slowly until clinical benefits are achieved in the absence of adverse events or until limited by adverse events.
B. Give each treatment an adequate trial. A clinical benefit may take as long as two to three months to manifest itself.
C. Avoid interfering medications (e.g., overuse of certain acute medications such as ergotamine).
D. Use of a long-acting formulation may improve compliance.

Patient education

A. Maximize compliance. Discuss with the patient the rationale for a particular treatment,

when and how to use it, and what adverse events are likely.
B. Address patient expectations. Discuss with the patient the expected benefits of therapy and how long it will take to achieve them.
C. Create a formal management plan

EVALUATION

A. Monitor the patients' headaches by having them keep headache diaries. Diaries help to track headache and related symptoms from one clinic visit to another. By consensus, they are considered the "gold standard" in headache attack evaluation. Diaries should be user-friendly and should measure attack frequency, severity, duration, disability, response to type of treatment, and adverse effects of medication.
B. Re-evaluate therapy. After a period of stability, consider tapering or discontinuing treatment.

Coexisting (comorbid) conditions

Some conditions are more common in persons with migraine. Take into account the presence of coexisting diseases. These include stroke,ss myocardial infarction, Raynaud's phenomenon, epilepsy, affective disorders, and anxiety disorders. Coexisting diseases present both treatment opportunities and limitations. For example:

A. Once the coexisting condition has been identified, select a pharmacological agent that will treat both disorders.
B. Establish that the coexisting condition is not a contraindication for the selected migraine therapies(e.g., beta-blockers are contraindicated in patients with asthma).
C. Establish that the treatments being used for coexisting conditions do not exacerbate migraine.
D. Beware of interactions between pharmacological agents used for migraine and those used for other conditions.
E. Direct special attention to women who are pregnant or want to become pregnant. Preventive medications may have teratogenic effects. If treatment is absolutely necessary, select a treatment with the lowest risk of adverse effects to the fetus.

Specific Treatment Recommendations [19, 20]

Individual medications have been put into treatment groups based on their established clinical efficacy, significant adverse events, safety profile, and clinical experience of the US Headache Consortium participants:

Group 1. Medications with proven high efficacy and mild-to-moderate adverse events.

Group 2. Medications with lower efficacy (i.e., limited number of studies, studies reporting conflicting results, efficacy suggesting only "modest" improvement) and mild-to-moderate adverse events.

Group 3. Medication use based on opinion, not randomized controlled trials.
a) mild-to-moderate adverse events,
b) frequent or severe adverse events (or safety concerns), complex management issues (special diets, high potential for severe adverse drug interactions, or drug holidays).

Group 4. Medication with proven efficacy but with frequent or severe adverse events (or safety concerns), or complex management issues (special diets, high potential for severe adverse drug interactions, or drug holidays).

Group 5. Medication proven to have limited or no efficacy.

Table 1

***provides a comprehensive review of the level and quality of scientific evidence found in the* literature and based on clinical experience. Treatments were included in a specific**

Migraine Without Aura

1. No aura or prodrome
2. Unilateral throbbing headache
3. May be accompanied by bnausea and vomiting

Migraine With Aura

1. Unilateral throbbing headache and later becomes generalized
2. Aura or prodrome is present
3. Patient complains of visual disturbances and may have mood variations

Migraine in Women[6]

Migraine is 2-3times more prevalent in women than in men after puberty and is often associated with menstrual period in women.

Early-morning Migraine

It is unpredictable in its occurrence and attack can start at any time of the day. However many patients report attacks that are fully developed on waking up in the morning.

Migraine in Children

Studies show that between half to three-quaters of children aged 12-17 years experience one or more headaches per month.

PATHOPHYSIOLOGY[7, 8, 9]

In the genetically susceptible patient, migraine can be initiated by a variety of specific triggers, including loud noises, stress, odors, lights, hunger, trauma, exercise, changes in sleep habits, menstruation, alcohol, nitrates, chocolate, caffeine, and other drugs and foods. It has also been suggested that a state of cortical hyperexcitability results in a reduced threshold for migraine attacks in the presence of specific internal or external triggers. Pharmacologic agents that stimulate presynaptic serotonin receptors (5-HT) on perivascular trigeminal sensory nerve fibers may inhibit the release of vasoactive neuropeptides such as calcitoningene- related peptide, neurokinin A, and substance P. Ergot derivatives and triptan drugs may be effective in migraine because they prevent the release of these mediators of inflammation, thus blocking dural vasodilation and plasma extravasation. Another possible mechanism of action of ergots and triptans is vasoconstriction resulting from direct stimulation of the postjunctional serotonin receptors (SHT) on meningeal, dural, and cerebral blood vessels. Because SHT, receptors are also present on noncranial vessels, coronary vasoconstriction is possible with these agents; thus ergots and triptans are contraindicated in patients with coronary artery disease.

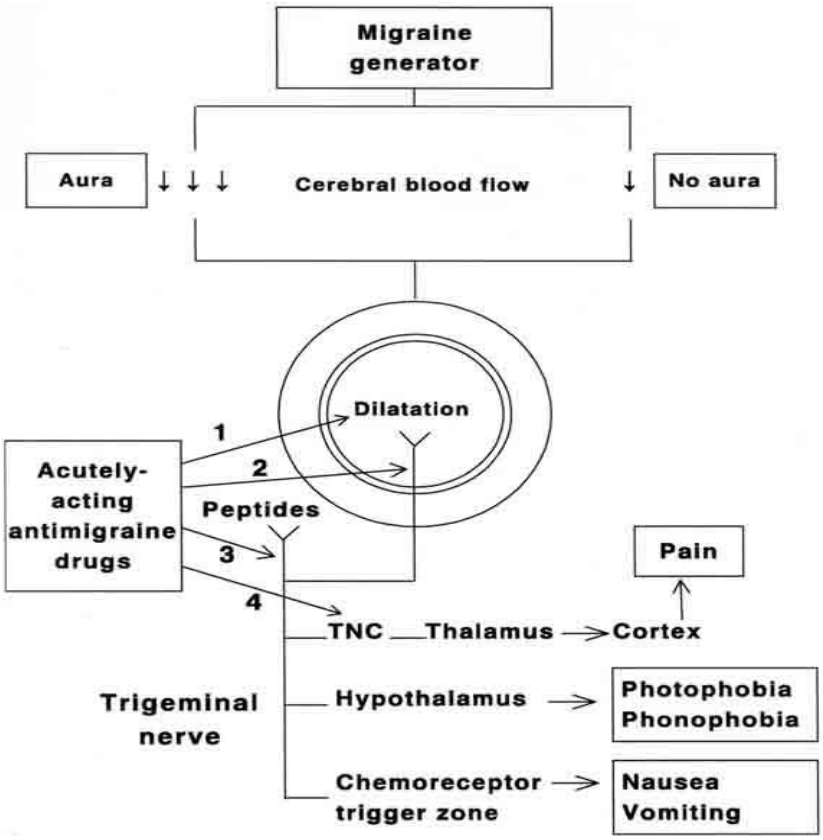

Fig.

Diagram showing putative changes in migraine and the therapeutic targets of acutely acting antimigraine drugs. These drugs are believed to owe their antimigraine efficacy to direct vasoconstriction of dilated cranial blood vessels (1), inhibition of trigeminally-induced cranial vasodilatation (2), plasma protein extravasation (3) and/or central neuronal activity (4). Only lipophilic, brain penetrant triptans (not sumatriptan) exert central trigeminal inhibitory effects[9].

VASCULAR THEORY[10, 11]

1. Intracerebral blood vessel vasoconstriction – aura
2. Intracranial/Extracranial blood vessel vasodilation – headache

SEROTONIN THEORY

1. Decreased serotonin levels linked to migraine
2. Specific serotonin receptors found in blood vessels of brain

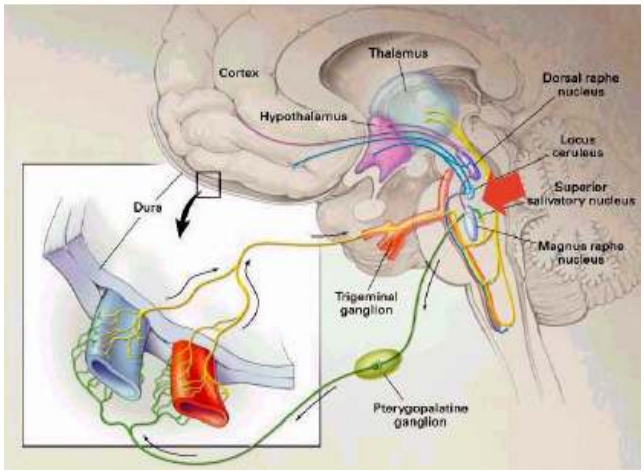

Figure 2
The Neuro vascular Theory

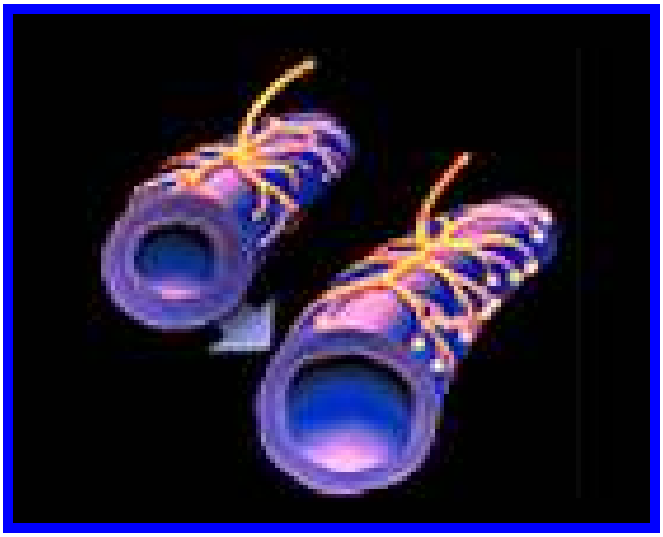

Figure 3
ArterialActivation

Figure 4

Release of Neurotransmitter

Figure 5
Worsening of Pain

Goals of Treatment for Prevention of Migraine

(1) Reduce attack frequency, severity, and duration;
(2) Improve responsiveness to treatment of acute attacks; and
(3) Improve function and reduce disability.

Investigations (only to exclude secondary causes)

a. EEG
b. CT Brain
c. MRI

TREATMENT OF MIGRAINE:

Variety of agents are available for the symptomatic treatment of migraine headache,including over-the-counter analgesics,nonsteroidal anti-inflammatory drugs (NSAIDs), combination products, opiates, ergot alkaloids, corticosteroids,dopamine antagonists, and triptans. In the stepped-care approach, simple analgesics and NSAIDs are the recommended first step for the treatment of mild-to-moderate migraine headaches. Patients who do notrespond to first-step treatments may be given ergots, combination products, dopamine antagonists, or triptans as the second step.

ABORTIVE THERAPY[12, 13, 14]

Non-specific treatment

DRUG	DOSE	ROUTE
Aspirin	500-650 mg	Oral
Paracetamol	500mg- 4 g	Oral
Ibuprofen	200- 300 mg	Oral
Diclofenac	50- 100mg	Oral/ IM
Naproxen	500- 750mg	Oral

Specific treatment

Ergot Alkaloids

Ergotamine	1mg-6g/d	Oral
Dihydroergotamine	0.75 - 1mg	SC

5-HT Receptor Agonist

Sumatriptan	25-300mg	Oral
	6mg	SC
Rizatriptan	10mg	Oral

ANTI-NAUSEANT DRUGS:

Domperidone	10-80mg	Oral
Metoclopramide	5-10mg	Oral/IV
Promethazine	50-125mg	Oral/IM
Chlorpromazine	10-25mg	Oral/IV

PREVENTIVE THERAPY FOR MIGRAINE

Drug	*Dose(mg/d)*
Betablockers	
Propranolol	40 – 320
Calcium Channel Blockers	
Flunarizine	10 – 20
Verapamil	120 – 480
TCAs	
Amitriptyline	10 – 20
SSRIs	
Fluoxetine	20 – 60
Anti –convulsant	
Sodium valproate	600 – 1200
Anti- Histaminic	
Cyproheptadine	4 – 8

Future trend in antimigraine therapy[20]:

Treatment modalities under investigation include:

1. New Triptans, some with novel mechanism of action
2. The combination of a Triptan with an analgesic or an Antiemetic to improve gastric motality has the potential to provide synergistic effect over and above Triptan alone.
3. The co-administration of a long half life triptan (eg. Naratriptan) together with a

faster acting Triptan(eg. Sumatriptan) has potential for the treatment of patients who frequently report headache recurrence following therapy.

4. Medications designed to inhibit the sterile neurogenic inflammation associated with migraine pathogenesis but which do not have significant vasoconstrictor effect. These drugs are hypothesised to be safer than the triptans, as they will have no significant cardiovascular effects.
5. Drugs that inhibit the the nitric oxide synthase enzyme reduce the level of nitric oxide and so inhibit the development of migraine attacks triggered by this compound.
6. Glutamate receptor antagonist show great potential as new acute treatment for migraine.
7. New prophylactic medication are also being developed, including Botulinum toxin TypeA (Botex), tizanidine, Montelukast and Rofecoxib.

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