Novel therapeutic approaches in management of migraine

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ABSTRACT

Migraine is neurological disorder greatly affecting the life of many peoples. Current management of migraine deals with Triptans, NSAID drugs. This drugs used in migraine or during attack. These drugs have their own merits and demerits. Preventive measure may not be effective all the times. Emerging drugs like Zonisamide, Levetiracetam, Carvedilol, Quetiapine showing good results. Novel therapeutic like Combination treatment of Sumatriptan-Naproxen, BIBN4096-Dihydroergotamine, Quetiapine-Zolmitriptan and Montelukast, Hydrosoluble Diclofenac epolamine making big impression in migraine treatment. Alternative medicine like Herbal Feverfew and Kudzu root proving effectiveness in therapy. New therapeutic delivery system giving more comfort to migraine patients. Drugs under clinical trial like CGRP antagonist will make difference. And time will come when migraine will no longer remain headache to mankind.

Keywords: Migraine, Sumatriptan-Naproxen, Feverfew, CGRP Antagonist.

INTRODUCTION

The word Migraine is French in origin and comes from Greek know as Hemicrania means Half the Head. Migraine is neurological disorder characterized by Pulsating Headache, usually restricted to one side, which comes in attacks lasting from 4 to 72 Hours. Migraine is recurrent headache separated by symptom free interval. Women’s are three times more likely than men to have migraine. Treatments such as triptans, NSAID are insufficient for migraine management. To overcome such problems many advances taken place in regimen from diagnosis to prevention which we will be discuss in detail in our article.

CLASSIFICATION

A. Migraine without Aura

It is also known as Common Migraine. Typical characteristics of this Headache are unilateral location, pulsating quality, moderate or severe intensity and association with nausea, photophobia and phonophobia. About 85% migraine people suffering from this type of migraine.

B. Migraine with Aura

It is also known as classical migraine. Headache is preceded by neurological symptoms called auras consisting of reversible visual, sensory symptoms. So it is reversible neurological type migraine in which aura develop gradually over 5-20 minutes and last for less than 60 minutes, after that “migraine without aura” symptoms followed. Nearly 15% migraine people have this type of migraine. Other types of migraine are:

1. Basilar type Migraine: It is formally known as basilar artery migraine (BAM) or Basilar Migraine (BM). It is an uncommon type of migraine with symptoms that results from brainstem dysfunction. Serious episodes of BAM can lead to stroke, coma or even death.
2. Familial Hemiplegic Migraine: It is caused by ion channel mutation. It is type of migraine with possible polygenic component. It shows headache accompanied by reversible limb weakness on one side as well as visual, sensory or speech difficulties.
3. Abdominal Migraine: It is recurrent disorder of unknown origin. It occurs mainly in children.
4. Menstrual Migraine: Its causes are uncertain but evidence suggests there may be link between menstruation and migraine due to drop in estrogens level. There are again 2 types of this Migraine –Menstrual related migraine (PMM) and pure menstrual migraine (4).

CAUSES

1. Stress
2. Foods
3. Sensory stimuli
4. Changes in wake-sleep pattern

SIGN AND SYMPTOMS

1. Prodrome Phase- Prodromal phase may consist may alter mood, irritability, depression, fatigue, stiff muscle, increased urination. The phase occurs hours or days before the headache.
2. Aura Phase- This aura comprises focal neurological phenomena that preceded or accompany attack. The headache phase of migraine attack usually begins with 60 minutes of the end of aura phase.
3. Pain Phase- Typical migraine headache is unilateral, throbbing and may be aggravated by physical activity. Pain may start on one side and become generalized. Head pain varies greatly in intensity. Nausea occurs in almost 90% of
patients, while vomiting occurs in about one third of patient.
4. Post drome Phase- Patient may feel tired, “Washed out”, irritable. Some people may feel unusually refreshed or euphoric after an attack. (5)

**PATHOPHYSIOLOGY**

The brain hypothesis links migraine to phenomenon of cortical spreading depression. (5) This is neuronal activity accompanied by reduced blood flow in posterior part of the cerebral hemisphere. This hypoperfusion gradually spreads over the surface of cortex to other area of brain. The hypoperfusion persist throughout aura and well into headache phase. (4) The vascular theory attributes intracerebral vasoconstriction causing the aura and the extra cerebral vasodilation phase causing headache.

The “Sensory Nerve” hypothesis suggests that activation of trigeminal in the meanings and extra cranial vessels is the primary event in migraine attack. This will cause release of neuropeptides (CGRP, SP) from sensory nerve terminals. (5)

**DIAGNOSIS**

In most cases no x-ray, blood tests are required to make diagnosis but in persons with severe headaches, neurological findings or complicated medical histories, the physician may recommended an MRI or CT scan.

**Computerized Tomography (CT)**

This imaging procedure uses a series of computer directed x-rays that provides across sectional view of brain.

**Magnetic Resonance Imaging (MRI)**

MRI use radio waves and powerful magnet to produce detailed cross-sectional view of brain. MRI can used to examine the blood vessels that supply the brain; MRI scans may reveal white matter lesions in young persons with migraine. (6)

**NEW DIAGNOSTIC APPROACHES**

1) Positron Emission Tomography (PET)

In this 3-D image of brain obtained. It is also use to measure brain function. Fluorine based radio-isotope is used during PET scan.

2) Computerised Headache assessment Tool (CHAT)

CHAT was developed using an expert system approach to headache diagnosis, with initial branch point determined by headache frequency and duration. CHAT was posted on a web site using Microsoft active server pages and SQL-server database server. The described expert system display high diagnosis accuracy for migraine. As a part of disease management program, CHAT led to patients receiving appropriate diagnoses. (5)

**CURRENT THERAPY**

- Acute treatment can be classified as non-specific and migraine specific. Non-specific treatment includes analgesic such as NSAID drugs and drugs such as prochlorperazine to control vomiting. Opioids are reserved as rescue medication when other treatments of severe migraine attack are not successful.

Specific migraine therapy includes triptan and dihydroergotamine.

- **Triptans:**
  This class of drug are 5HT-1D receptor agonist. It has been proposed that activation of 5HT-1D receptor by these agents leads either to vasoconstrictor or to inhibition of the release of proinflammatory neuropeptides. These agents rapidly and effectively abort the severity of migraine headaches in about 70% of patients. The drug has short duration of action. Headache commonly recurs within 24 to 48 hrs after single dose of drug but in most patients a second dose is effective in aborting headache.

- **Dihydroergotamine:**
  It is a derivative of ergotamine. It is administered intravenously and has an efficacy similar to that of Sumatriptan, but nausea is a common adverse effect. (5)

**Triptan formulation for acute treatment of migraine.**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Formulation</th>
<th>Dose (mg)</th>
<th>Max. Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>Oral tablet</td>
<td>25,50,100</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>Nasal spray</td>
<td>5,20</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>S.C. Injection</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Oral tablet</td>
<td>2,5,5</td>
<td>10</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>Oral tablet</td>
<td>5,10</td>
<td>30</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>Tablet</td>
<td>1,2,5</td>
<td>5</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>Tablet</td>
<td>20,40</td>
<td>80</td>
</tr>
</tbody>
</table>

**Prophylaxis treatment**

Regular medication to reduce the frequency and or severity of attacks is recommended for moderate to severe migraine when more than 2-3 attacks occur per month. Diverse classes of drugs are used but none is effective in all cases and none abolishes the attack totally. It may prudent to discontinue prophylaxis every 6 month to check whether its continuation is needed or not. (12)

<table>
<thead>
<tr>
<th>Use</th>
<th>Drug</th>
<th>Mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis</td>
<td>Pizotilens (0.5-2mg daily)</td>
<td>5HT receptor antagonist muscarinic acetylcholine antagonist.</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Methysergide (1-4mg)</td>
<td>Receptor antagonist/partial antagonist. ( 5HT 2)</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Cyproheptadine</td>
<td>5HT2 receptor antagonist</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Propanolol (40-120mg)</td>
<td>Mechanism is not clear.</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Twice a daily</td>
<td></td>
</tr>
</tbody>
</table>

**EMERGING DRUGS FOR MIGRAINE TREATMENT**

1. **TPM:**
   It was recently approved by USFDA for migraine prophylaxis. It is neuromodulator with a structurally unique formula that provides mechanisms of action and can influence the activity of some types of voltage activated Na+ and Ca++ channels, the GABA-A receptor, AMPA/Kainite subtype of glutamate receptors. It has been postulated that TPM may bind to membrane channel complexes and modulate the ionic conductance through the channels. The best re-
result was achieved at doses of 100mg or 200mg, with no difference in efficacy observed between 2 doses. It is considered a preferred treatment for all patients migraines who are concerned about gaining weight, who are current overweight or have coexisting epilepsy. TPM may be useful for paediatric migraines as well.

2. Zonisamide:

It is sulphamamide derivative that is structurally and chemically unrelated to other AEDs. It has been used for partial seizures. It represents unique combination of pharmacologic actions. It blocks voltage gated sodium and T- (but not L-type) calcium channels, reduces glutamate-mediated excitatory neurotransmission, inhibits excessive nitric oxide (NO) production. All of this mechanism may play role in headache and pain modulation possibly via neurostabilization. Headache severity was significantly reduced as well as other headache measures.

3. Levetiracetam (LCT):

It is new AED of unknown mechanism of action. Evidences suggest the usefulness of LCT in the prevention of migraine. A recent study assessed LCT as prophyaxis of transformed type of migraine. It is rapidly and nearly completely absorbed after oral administration, peak serum concentration is achieved within 2 hours.

4. Carvedilol:

The use of beta blocker for migraine prevention is not new. The evidence for use of this pharmacological class was well established with propanolol, timolol, atenolol. The use of new beta blocker such as carvedilol for the prophylactic treatment of migraine is new concept because it offers additional a-1 blocking and antioxidant properties.

5. Tizanidine:

Tizanidine hydrochloride is a-2 adrenergic presynaptic agonist that inhibits the release of norepinephrine in the brainstem and spinal cord. Tizanidine a-2 adrenergic presynaptic agonist that has been advocated for migraine prophyaxis.

6. Quetiapine:

QTP represent a new hope for migraineurs because it also possesses high affinity for 5-HT, receptors, partial agonistic activity at 5HT 1 receptors and a blocking activity at a-1 adrenergic receptors with a consequent potential for migraine prevention. The clinical impression is that QTP represent important resource for patient with refractory migraine. (8)

NOVEL THERAPEUTIC APPROACH
Sumatriptan- Naproxen Combination:

Neurology researchers identified a new, more potent therapy to relieve often debilitating symptoms of migraine. They found that combining two different types of treatment of above medications gives better result rather than single drug therapy. Sumatriptan 85mg + Naproxen 200mg, investigators evaluated the effectiveness and safety of combine drugs and compared with placebo and either of those drugs individually. They found that sumatriptan-naproxen sodium therapy was superior to sumatriptan monotherapy and placebo in sustained pain free response from 2 hours. A major benefit is that this therapy targets more than one migraine mechanism so it shuts the migraine down rapidly and effectively. (9)

BIBN4096 Combination With dihydroergotamine:

BIBN 4096 acts as Calcitonin gene related peptide (CGRP) antagonist. A method of treatment or prevention of migraine comprises co-administration of BIBN 4096 or its salt with second active antimigraine drug, particularly Sumatriptan, Zolmitriptan, or dihydroergotamine. (10)

Combination of Quetiapine and Zolmitriptan:
The present combination comprising quetiapine or zolmitriptan or its salt use in the manufacture of a medicament. This combination of drugs is use for migraine treatment. Both drugs are different one may use for disorder typically treated with 5HT agonists and other for atypical antipsychotic. It will acts by reducing or eliminating of migraine recurrence. (11)

Montelukast:
Leukotriens and other inflammatory mediators involved in inflammatory cascade believed to be associated with pathophysiology of migraine. NSAID used widely in treatment of migraine. It is reasonable to think that medications that could antagonize leukotriene functions could be effective in migraine prevention. The clinical observation of a decrease in migraine frequency in patients with asthma taking montelukast a specific D4 leucotriene receptor antagonist, lead to first open study, using Montelukast sodium 20 mg in the prevention of migraine. (12)

Hydrosoluble Diclofenac Epolamine:
It represents an interesting approach to acute migraine attack, where gastrointestinal motility and drug absorption are often reduced. Time to attack resolution, light and noise sensitivity and impact on working ability of human beings were significantly reduced by DHEP compared with placebo. No adverse reaction was recorded. DHEP was effective and safe for pain relief in patients with acute, mild to moderate migraine attacks. (13)

Donitriptan:
It is a piperazide 5-HT1D agonist. In January 2001, Donitriptan had completed phase I trials for migraine and was then enter in phase II development. This compound has an increased potency, markedly higher intrinsic activity in comparison to the well described tryptamine derivatives, naratriptan, zolmitriptan and sumatriptan. (14)

N-a-methyl histamine-The histamine catabolite N-a-methyl histamine, possesses a selective affinity for H-3 receptors. The S.C. administration of N-a-methyl histamine 1-3ng twice a week against placebo studied. Study provided evidence of the N-a-methyl histamine given S.C. at dose 1-3ng twice a week, showed safety and efficacy in clinical trials. Offering a new therapeutic alternative in migraine prophylaxis. (15)

Tramadol/Acetaminophen:
Tramadol/Acetaminophen reduces the severity of pain, photophobia and phonophobia associated with migraine headache. Tramadol/Acetaminophen gives better results so it can be appropriate option for the management of moderate to severe type of migraine headache. (16)

Baclofen:
Baclofen, an analogue of the putative inhibitory neurotransmitter- amino butyric acid is capable of crossing blood brain barrier. It acts centrally via GABA receptors in migraine. In the open study
baclofen was found to be prophylactic for migraine.\(^{(17)}\)

**Botulinum Toxin:**

The mechanism by which botulimum toxin A may be work to prevent headache is not clear. BoNTA may be a useful treatment option for headache patients demonstrating poor compliance, adverse effect profile with oral prophylactic regimens.\(^{(18)}\)

**ALTERNATIVE TREATMENTS**

**1. Melatonin:**

Researcher has found pineal hormone melatonin is low in migraine patients. Additionally several studies required to use melatonin as future treatments in Migraine patients.\(^{(19)}\) A-lipolic acid- In this use of racemes a lipolic acid or its enantiomers or its salts in reduced or oxidized form act as active ingredients in the prevention of acute treatment of migraine.\(^{(20)}\)

**2. Herbal Treatments**

*Petasites hybridus root* (butterbur):

Study was performed over 4 months of treatment, in the per-protocol analysis in migraine sufferers, migraine attack frequency was reduced by 48% for Petasites extract 75 mg bid. Petasites extract 75 mg bid is more effective than placebo. So it can be use as effective preventive measure for migraine.\(^{(21)}\)

*Tanacetum parthenium* (Feverfew):

It is a well-known herb for the prophylactic treatment of migraine. A dose-response of a new stable extract (MIG-99) reproducibly manufactured with supercritical CO2 from feverfl (T. parthenium). The study provided data on the safety and tolerability of MIG-99. In a randomized, double-blind, multicentre, controlled trial with an adaptive design, the clinical efficacy and safety of three dosages of MIG-99 (2.08 mg; 6.25 mg; 18.75 mg t.i.d.) were compared with placebo. MIG-99 was shown to be effective only in a small predefined sub-group of patients with at least four attacks during the 28-day baseline period where the most favourable benefit was observed with a dosage of three capsules of 6.25 mg MIG-99 extract per day.\(^{(22)}\)

*Pueraria lobata* (Kudzu root):

It has been used for centuries in traditional Chinese medicine in the form of Pueraria radix (0.02-2%), an isoflavone-rich extract derived from roots of P. lobata, to treat a variety of conditions including pain, allergies, angina, alcoholism and Migraine.\(^{(23)}\)

**Cannabis:**

Cannabis or marijuana has been used for centuries for both symptomatic and prophylactic treatment of migraine. It was highly esteemed as a headache remedy by the most prominent physicians of the age between 1874 and 1942. But due to its narcotics nature use may be restricted.\(^{(24)}\)

**MIGRAINE MANAGEMENT: NEW HORIZONES**

**1. Mobile web-based monitoring**

The internet can facilitate daily monitoring (experience sampling, ecologic assessment) and behavioural coaching. Online digital assistance (ODA) is a generic tool for mobile web-based use, intended as an adjuvant to face or internet-based cognitive behavioural treatment. A current ODA application was designed to support home-based training of prevention in chronic migraine, focusing on identification of attack precursors and the support of preventive health behaviours. ODA combines mobile electronic diary monitoring with direct human online coaching of health behaviour according to the information from the diary. The diary contains three parts (1) medication use (2) attack precursors and (3) self-relaxation and other preventive behaviour. ODA is feasible and well accepted ODA offers generic tool to combine mobile coaching with diary monitoring, independently of time and space.\(^{(25)}\)

2. **New Therapeutics Deliverers in Migraine**

**Intranasal route:** Tablets are highly effective and convenient but may not be suitable in migraine those suffers from nausea, vomiting and gastric disturbances. Intranasal route of administration appears to be an obvious way to deliver a migraine treatment. Sumatriptan is a highly effective treatment for migraine in adults but its efficacy in children had also been proved. Another drug is Civamide vanilloid receptor agonist and neuronal calcium channel blocker that inhibit the neuronal release of excitatory neurotransmitters CGRP and substance P (SP). Based upon the results of study it indicated intranasal civamide may be effective in the acute treatment of migraine headache.\(^{(26)}\)

**BSPCI-** It is breath synchronised plume-control inhaler (BSPCI). It is used to deliver ergotamine tartarate.Open label studies; the BSPCI allows rapid delivery of potentially therapeutic plasma concentrations of ergotamine tartarate. This system can be use for delivery of anti-migraine drugs.\(^{(28)}\)

**NXN 188:**

NeurAxon, Inc., a developer of next generation pain therapeutics targeting neuronal nitric oxide synthase (nNOS) announced positive data from its phase II clinical trial assessing safety of drug candidate. NXN-188 is a first in class, dual action small molecule that is being developed for the treatment of acute migraine and which incorporates both 5HT agonism and NOS inhibition can relieve pain.\(^{(29)}\)

**Tezampanel:**

Torrey pines Therapeutics, Inc. Tezampanel met the primary endpoint in patient with, phase II clinical trial of a single, acute migraine attack. In this study tezampanel S.C, 40 mg dose demonstrated statically significant improvement in pain response compared to placebo and the response was sustained through 2 hours and gives pain relief from acute migraine.\(^{(30)}\)

**AZ-104:**

Alexza Pharmaceuticals announced that it has initiated a Phase 2b clinical trial with AZ-104 (Staccato loxapine) in patients with migraine headaches. Alexza believes that AZ-104 could be effective and safe in comparison to triptans, which are the most commonly, used class of therapeutics targeting neuronal nitric oxide synthase (nNOS) announced positive data from its phase II clinical trial assessing safety of drug candidate. NXN-188 is a first in class, dual action small molecule that is being developed for the treatment of acute migraine and which incorporates both 5HT agonism and NOS inhibition can relieve pain.\(^{(31)}\)

**NGX 426:**

NGX426 is an oral prodrug of tezampanel. In study, NGX426 has been shown to rapidly convert to tezampanel. In this clinical trial NGX426 demonstrated a statistically significant reduction in spontaneous pain, hyperalgesia and allodynia compared to placebo following intradermal injections of capsaicin.\(^{(32)}\)

**MK-0974:**

Clinical results from a phase II study showed that MK-0974 an investigational oral calcitonin gene related peptide (CGRP) receptor antagonist, significantly improved migraine pain relief two hours
after dosing compared to placebo and relief was sustained through 24 hours. MK-0974 is an antagonist of the receptor for CGRP. A primary neuropeptide involved in the, pathophysiology of migraine. CGRP and its receptors are found in areas of the central and peripheral nervous system that are important for transmission of impulse. MK-0974 blocks binding of CGRP to receptors within these areas and thereby inhibits transmission of pain signals that lead to migraine. 

CONCLUSION

The migraine management only possible when ideal migraine drugs should be effective for both prophylaxis and treatment. After available clinical studies we come to know TPM seems promising drugs should be effective for both prophylaxis and treatment. After

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