Therapy of Migraine

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Migraine Headache

Pathophysiology:

- Mechanisms of migraine are not completely understood.
- Vasodilation of intracranial extracerebral blood vessels results in the activation of the perivascular trigeminal nerves that release vasoactive neuropeptides (calcitonin gene-related peptide (CGRP), neurokinin A, and substance P) from perivascular axons.
- The released neuropeptides interact with dural blood vessels to promote vasodilation and dural plasma extravasation, resulting in neurogenic inflammation.

Migraine Headache

- **Continued afferent input can result in sensitization of the central sensory neurons, producing a hyperalgesic state that responds to previously innocuous stimuli and maintains the headache.**
- **Activation of central pain transmission and other brainstem nuclei results in associated symptoms (nausea, vomiting, photophobia, and phonophobia).**

Migraine Headache

- 5-HT receptors are implicated in the pathophysiology of migraine headache.
- Specific antimigraine drugs (ergot alkaloids and triptans) are agonists at vascular and neuronal 5-HT_1 receptor subtypes, → vasoconstriction of meningeal blood vessels and inhibition of vasoactive neuropeptide release and pain signal transmission.

Migraine Therapy

Commonly Reported Triggers of Migraine:

A. Food triggers:

- Alcohol
- Caffeine/caffeine withdrawal
- Chocolate
- Fermented and pickled foods
- Monosodium glutamate (in Chinese food, seasoned salt, and instant foods)
- Nitrate-containing foods (processed meats)
- Saccharin/aspartame (diet foods or diet sodas)
- Tyramine-containing foods

Migraine Therapy

B. Environmental triggers:

- Glare or flickering lights
- High altitude
- Loud noises
- Strong smells and fumes
- Tobacco smoke
- Weather changes

C. Hormones:

- Changes in estrogen levels (menarche, menstruation, pregnancy, menopause, and oral contraceptive use) can trigger, intensify, or alleviate migraine. A drop in estrogen precipitates attacks.

Migraine Therapy

D. Behavioral/Physiologic triggers:

- **Excess or insufficient sleep**
- **Fatigue**
- **Menstruation, menopause**
- **Sexual activity**
- **Skipped meals**
- **Strenuous physical activity (prolonged overexertion)**
- **Stress or post-stress**

Migraine Therapy

Goals of acute migraine treatment:

1. Terminate migraine attacks rapidly.
2. Reduce recurrence rate significantly.
3. Restore the patient's ability to function normally.
4. Cause minimal or no therapy-related adverse effects.

Migraine Therapy

Goals of long-term migraine treatment:

1. **Reduce migraine frequency, severity, and disability.**
2. **Reduce reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies.**
3. **Improve quality of life.**
4. **Prevent headache.**
5. **Avoid escalation of headache-medication use.**
6. **Educate and enable patients to manage their disease.**
7. **Reduce headache-related distress and psychological symptoms.**

Migraine Therapy

General Approach to Treatment:

- Drug therapy is the mainstay of treatment for most patients.
- Pharmacotherapeutic management of migraine can be acute (abortive) or preventive .
- Coexisting illnesses can limit and/or dictate treatment choices.
- Abortive or acute therapies can be migraine-specific (ergots and triptans) or nonspecific (analgesics, antiemetics, nonsteroidal antiinflammatory drugs [NSAIDs], and corticosteroids).
- These drugs are most effective when administered at the onset of migraine.

Migraine Therapy

- **Initial treatment is based on headache-related disability and symptom severity.**
- **It is advised to use nonspecific agents for mild - moderate headache NOT causing disability while reserving migraine-specific medications for more severe attacks.**
- **The absorption and efficacy of orally administered drugs can be compromised by gastric stasis or nausea and vomiting that accompany migraine.**
- **Therefore, pretreatment with antiemetic agents or the use of non-oral treatment (suppositories, nasal sprays, or injections) is advisable when nausea and vomiting are severe.**

Migraine Therapy

Analgesics:

- **Acetaminophen**

Nonsteroidal antiinflammatory drugs:

- **Aspirin, Ibuprofen, Naproxen, Diclofenac.**

Ergot alkaloids:

- **Ergotamine/caffeine, Dihydroergotamine**

Serotonin agonists (triptans):

- **Sumatriptan, Zolmitriptan, Rizatriptan, Almotriptan, Frovatriptan, Eletriptan.**

Miscellaneous:

- **Metoclopramide, Prochlorperazine.**

Migraine Therapy

- **The frequent or excessive use of acute migraine medications can result in medication-overuse headache (or rebound headache).**
- **In this case the headache returns as the medication is eliminated, leading to use of more drug for relief.**
- **The patient experiences a daily or near-daily headache with superimposed episodic migraine attacks.**

Migraine Therapy

- **Discontinuation of the offending agent leads to a gradual decrease in headache frequency and severity and a return of the original headache characteristics.**
- **Detoxification can be accomplished on an outpatient basis.**
- **Hospitalization may be necessary for the control of refractory rebound headache and other withdrawal symptoms (nausea, vomiting, asthenia, restlessness, and agitation).**

Migraine Therapy

- **Regulation of nociceptive systems and renewed responsiveness to therapy usually occur within 2 months following medication withdrawal.**
- **It is recommend to limit the use of acute migraine therapies to < 10 days per month to avoid the development of medication-overuse headache.**
- **Preventive migraine therapies are administered on a daily basis to reduce the frequency, severity, and duration of attacks and improve responsiveness to symptomatic migraine therapies.**

Pharmacologic Management of Acute Migraine

Analgesics and NSAIDs:

- **Simple analgesics and NSAIDs are effective and are first-line choice for treatment of mild-to-moderate migraine attacks.**
- **Of the NSAIDs, aspirin, diclofenac, ibuprofen, naproxen sodium, and the combination of acetaminophen plus aspirin / caffeine have demonstrated the most consistent evidence of efficacy.**
- **Acetaminophen alone is not generally recommended.**

Pharmacologic Management of Acute Migraine

- **NSAIDs prevent inflammation in the trigeminovascular system through the inhibition of prostaglandin synthesis.**
- **Metoclopramide increases the absorption of analgesics and alleviate migraine-related nausea and vomiting.**
- **Suppository analgesic preparations are an option when nausea and vomiting are severe.**
- **Monitor for NSAIDs adverse reactions: Gastrointestinal (previous ulcer disease), CNS (somnolence, dizziness), renal disease, or hypersensitivity reactions, cardiovascular (hypertension, heart failure), ……**

Pharmacologic Management of Acute Migraine

Antiemetics:

- Adjunctive antiemetic therapy is useful for combating the nausea and vomiting of migraine headaches and that of medications used to treat attacks (ergotamine tartrate).
- Use single dose antiemetic (metoclopramide, droperidol, prochlorperazine), 15 - 30 minutes before ingestion of oral abortive migraine medications.
- Metoclopramide is also useful to reverse gastroparesis and improve absorption from the GI tract during severe attacks.

Pharmacologic Management of Acute Migraine

- In addition to antiemetic effects, dopamine antagonist drugs also have been used successfully as monotherapy for the treatment of intractable headache, or treatment of refractory migraine.
- Adverse effects include: drowsiness and dizziness, extrapyramidal adverse effects, and droperidol has a risk for QT prolongation.

Pharmacologic Management of Acute Migraine

Miscellaneous Nonspecific Medications:

1. **Corticosteroids can be considered as rescue therapy for status migrainous (a severe, continuous migraine that can last up to 1 week). IV or intramuscular dexamethasone at a dose of 10 - 25 mg has also been used as an adjunct to abortive therapy.**
2. **IV valproate 500 - 1,000 mg and magnesium sulfate 1,000 mg are nonsedating options for use in acute migraine treatment.**

Pharmacologic Management of Acute Migraine

Ergot Alkaloids:

- **Ergotamine tartrate and dihydroergotamine can be used in moderate-to-severe migraine attacks.**
- **They are nonselective 5-HT_1 receptor agonists that constrict intracranial blood vessels and inhibit the development of neurogenic inflammation in the trigeminovascular system.**
- **Ergotamine tartrate is available for oral, sublingual, and rectal administration.**
- **Oral and rectal preparations contain caffeine to enhance absorption and potentiate analgesia.**

Pharmacologic Management of Acute Migraine

- **Dihydroergotamine is available for intranasal, intramuscular, subcutaneous, and IV routes.**
- **Mixing with 1-2% lidocaine can reduce burning at the injection site.**

Adverse effects:

1. **Nausea and vomiting (resulting from stimulation of the chemoreceptor trigger zone) are among the most common adverse effects of the ergotamine derivatives. Therefore, their use requires pretreatment with antiemetic agents.**

Pharmacologic Management of Acute Migraine

2. Abdominal pain, weakness, fatigue, paresthesias, muscle pain, diarrhea, and chest tightness (are common).
3. Severe ischemia include: cold, numb, painful extremities, continuous paresthesias, diminished peripheral pulses, claudication and gangrenous extremities. Myocardial infarction, hepatic necrosis, and bowel and brain ischemia have also been reported.

Pharmacologic Management of Acute Migraine

4. **Ergotamine derivatives are contraindicated in patients with renal or hepatic failure; coronary, cerebral, or peripheral vascular disease; uncontrolled hypertension; and sepsis; and in women who are pregnant or nursing.**
5. **Rebound headache: more with ergotamine tartrate than dihydroergotamine.**

Pharmacologic Management of Acute Migraine

Serotonin Receptor Agonists (Triptans):

- **They represent a significant advance in migraine pharmacotherapy.**
- **The first member of this class, sumatriptan, and the second-generation agents zolmitriptan, rizatriptan, almotriptan, eletriptan, frovatriptan, and naratriptan are selective agonists at the 5-HT_{1B} and 5-HT_{1D} receptors.**
- **The triptans are appropriate first-line therapy for patients with mild to severe migraine and are used for rescue therapy when nonspecific medications are ineffective.**

Pharmacologic Management of Acute Migraine

Relief of migraine headache is the result of three key actions:

1) **Normalization of dilated intracranial arteries through enhanced vasoconstriction.**
2) **Inhibition of vasoactive peptide release from perivascular trigeminal neurons.**
3) **Inhibition of transmission through second-order neurons ascending to the thalamus.**

Pharmacologic Management of Acute Migraine

- Sumatriptan is available for subcutaneous, oral, and intranasal administration.
- Subcutaneous and intranasal sumatriptan have a more rapid onset of action than the oral formulation.
- It is available as an autoinjector device for self-administration.
- In general, triptans can be divided into those with a faster onset and higher efficacy and those with a slower onset and lower efficacy.

Pharmacologic Management of Acute Migraine

- **Compared with other triptans, frovatriptan and naratriptan have the longest half-lives, the slowest onset of action, and less headache recurrence.**
- **Faster-acting triptans are more efficacious when a rapid onset is necessary.**
- **Individual responses cannot be predicted, and if one triptan fails, a patient can be switched successfully to another triptan.**

Pharmacologic Management of Acute Migraine

Adverse effects:

1. **Paresthesias, fatigue, dizziness, and somnolence.**
2. **Flushing and warm sensations probably due to vasomotor autonomic dysfunction or part of migraine.**
3. **Local adverse effects are subcutaneous injection site reactions and taste perversion, nasal discomfort after intranasal use.**
4. **"Triptan sensations," including tightness, pressure, heaviness, or pain in the chest, neck, or throat.**
5. **Frequent use of the triptans has been associated with the development of medication-overuse headache.**

Pharmacologic Management of Acute Migraine

Contraindications:

1. **History of ischemic heart disease (angina pectoris, Prinzmetal's angina, or previous myocardial infarction), uncontrolled hypertension, cerebrovascular disease, and hepatic diseases.**

- **Postmenopausal women, men older than 40 years of age, and patients with uncontrolled risk factors should receive a cardiovascular assessment prior to triptan use and have initial doses administered under medical supervision.**

2. **Hemiplegic and basilar migraine.**
3. **Pregnancy (category C).**

Pharmacologic Management of Acute Migraine

Drug Interactions:

1. **The triptans should NOT be given within 24 hours of the ergotamine derivatives.**
2. **Administration of sumatriptan, rizatriptan, and zolmitriptan within 2 weeks of therapy with monoamine oxidase inhibitors (MAOIs) is NOT recommended. (MAOIs slow triptan's metabolism).**
3. **Eletriptan should NOT be administered with cytochrome P450 3A4 inhibitors such as macrolide antibiotics, antifungals, and some antiviral therapies.**

Pharmacologic Management of Acute Migraine

4. **Concomitant therapy with the selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) (duloxetine, venlafaxine, and mirtazapine) can potentially cause "Serotonin syndrome".**

Migraine Prevention

β-Adrenergic antagonists:

- **Propranolol, Atenolol, Metoprolol XL, Nadolol.**

Anticonvulsants:

- **Topiramate, Valproic acid.**

Antidepressants:

- **Amitriptyline, Venlafaxine**.

Nonsteroidal antiinflammatory drugs:

- **Ibuprofen, Ketoprofen, Naproxen**

Serotonin agonists (triptans):

- **Frovatriptan, Naratriptan, Zolmitriptan.**
- others

Migraine Prevention

- **Preventive therapy should be considered in the following cases:**

1) **Recurring migraines that produce significant disability despite acute therapy.**
2) **Frequent attacks occurring more than twice per week with the risk of developing medication-overuse headache.**
3) **Symptomatic therapies that are ineffective or contraindicated, or produce serious adverse effects.**

Migraine Prevention

4) **Uncommon migraine variants that cause profound disruption and/or risk of permanent neurologic injury (hemiplegic migraine, basilar migraine, and migraine with prolonged aura).**
5) **Preventive therapy also may be administered intermittently when headaches recur in a predictable pattern (exercise-induced migraine or menstrual migraine).**
6) **Patient's preference.**

Migraine Prevention

- Only propranolol, timolol, divalproex sodium, and topiramate have established efficacy, although other agents may be effective.
- The selection of an agent typically is based on its adverse effect profile and the patient's coexisting comorbid conditions.
- 2 - 3 months are needed to achieve clinical benefit, but some reduction in attack frequency can be evident by the first month of therapy.
- Maximal benefits are typically observed by 6 months of treatment.

Migraine Prevention

- Drug therapy should be initiated with low doses and gradually increased until a therapeutic effect is achieved or side effects become intolerable.
- Drug doses for migraine prophylaxis are often lower than those necessary for other indications.
- Overuse of acute headache medications will interfere with the effects of preventive treatment.
- Prophylactic treatment usually is continued for at least 6 - 12 months after the frequency and severity of headaches have diminished, then gradual tapering or discontinuation may be reasonable.

Prophylactic Pharmacologic Therapy of Migraine

β-Adrenergic Antagonists:

- Are among the most widely used drugs for migraine prophylaxis.
- Metoprolol, propranolol, and timolol reduce the frequency of attacks by 50% in greater than 50% of patients.
- Their precise mechanism of antimigraine action is unknown.
- Adverse effects can include: drowsiness, fatigue, sleep disturbances, vivid dreams, memory disturbance, depression, impotence, bradycardia, atrioventricular conduction disturbances, heart failure, hypotension, bronchoconstriction.

Prophylactic Pharmacologic Therapy of Migraine

Antidepressants:

- The beneficial effects of antidepressants in migraine are independent of their antidepressant activity and may be related to downregulation of central 5-HT_2 receptors, increased levels of synaptic norepinephrine, and enhanced endogenous opioid receptor actions.
- The tricyclic antidepressant (TCA) amitriptyline and SNRI venlafaxine are classified as probably effective for migraine prophylaxis.
- Adverse effects: see the lecture on therapy of depression.

Prophylactic Pharmacologic Therapy of Migraine

Anticonvulsants:

- **The anticonvulsants valproate, divalproex, and topiramate all having established prophylactic efficacy.**
- **<u>The beneficial effects of valproate may be due to</u>:**

1) **Enhancement of GABA-mediated inhibition.**
2) **Modulation of the excitatory neurotransmitter glutamate.**
3) **Inhibition of sodium and calcium ion channel activity.**

- **They are particularly useful in patients with comorbid seizures, anxiety disorder, or bipolar illness.**

Prophylactic Pharmacologic Therapy of Migraine

- Topiramate is the most extensively studied medication for migraine prophylaxis.
- The benefits of topiramate are observed as early as 2 weeks after initiation of therapy, with significant reductions in migraine frequency within the first month.
- ~ 50% of patients treated have 50% or greater reduction in mean headache frequency.
- Adverse effects of these antiseizure drugs was discussed before.

Prophylactic Pharmacologic Therapy of Migraine

Triptans:

- Triptans are also useful for the prevention of menstrual migraine.
- The triptan is usually started 1 - 2 days before the expected onset of headache and continued during the period of vulnerability.
- Frovatriptan has established efficacy, while naratriptan and zolmitriptan are probably effective.