Therapy of Migraine

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Migraine Headache

Pathophysiology:

- Mechanisms of migraine are not completely understood.
- Vasodilation of intracranial extracerebral ("meningeal blood vessels") 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

through trigeminal N.

- **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:

→ Drops in it not increases

- 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.**

Bc most of those drugs have severe 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.

A serious problem in migraine pt
بشعر إنه لازم ياخذ الدوا ليروح الصداع
فيصير عنده over use.
تقصير نهاية ال dosing interval

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 attack.

• e.g: Triptan CI → IHD
Ergot CI → = alkaloids

old

new

against 5HT receptors

Due to vomiting from migraine and from other drugs of migraine (as an adverse effect)

Migraine Therapy

- Initial treatment is based on headache-related disability and symptom severity.
- It is advised to use nonspecific agents (NSAIDs) 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** Never good alone here

Nonsteroidal antiinflammatory drugs:

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

Ergot alkaloids: → improves absorption of ergotamine.

- **(Ergotamine/caffeine) Dihydroergotamine**

Serotonin agonists (triptans):

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

The prototype

Frova- + Nara- slow acting with low efficacy ↳ Good for prevention.

Miscellaneous: Antiemetics

- **Metoclopramide, Prochlorperazine.**

Migraine Therapy

at the end of dose interval.

- 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.

* صداع أسوأ من اللي بلشنا نعالج فيه في البداية، لازم نعلم المريض كيفية باخذ الأدوية

* Tx of medication-overuse headache

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. if you're lucky
- Hospitalization may be necessary for the control of refractory rebound headache and other withdrawal symptoms (nausea, vomiting, asthenia, restlessness, and agitation).

after Tx of medication-overuse headache →

Migraine Therapy

- Regulation of nociceptive systems and renewed responsiveness to therapy usually occur within 2 months following medication withdrawal.
- ** v.imp It is recommend to limit the use of Abortive 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. (1) (2)
  - Bc its a prokinetic agents, ↓ stasis ↑ gastric emptying, drug goes to intestines (absorption site)
- 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

vasodilation → leakage → inflammation → transmission of nerve pulses to high centers

Ergot Alkaloids: old drugs

- **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.**

Cafergot (ergot + caffeine)

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** (m.c) **(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. imp
5. Rebound headache: more with ergotamine tartrate than dihydroergotamine.

Pharmacologic Management of Acute Migraine

Serotonin Receptor Agonists (Triptans): The most effective antimigraine drugs

- 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.**

prototype

Ultra rapid acting (أسرع دواء)

(fast onset + high efficacy)

→ for prevention. (Slow onset + low efficacy)

2 NSAIDs .. etc.

- Best used for moderate-severe migraine, although they're used to treat or rescue any

migraine

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.** ∴ no extravasation, no inflammation
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

Ultra rapid acting

- **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.**

- Nose is a good absorptive area of drugs (Get absorped rapidly) but it's a small area (Small amounts are absorped) ↳unlike oral route.
- Nasal formulation causes irritation to the nasal mucosa.

chloramphenicol is rapidly absorped

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. (Bc of prolonged action (long t1/2))
- 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.

Bc high risk of IHD

2. Hemiplegic and basilar migraine.

Bc this migraine is caused by vasoconstriction! so you don't want to increase it

3. Pregnancy (category C).

We don't know about their adverse rxns yet.

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

1. **β-Adrenergic antagonists:**
   - **Propranolol, Atenolol, Metoprolol XL, Nadolol.**
2. **Anticonvulsants:**
   - **Topiramate, Valproic acid.**
3. **Antidepressants:**
   - **Amitriptyline, Venlafaxine.**
4. **Nonsteroidal antiinflammatory drugs:**
   - **Ibuprofen, Ketoprofen, Naproxen**
5. **Serotonin agonists (triptans):**
   - **Frovatriptan, Naratriptan, Zolmitriptan.**
   - others

slow fast

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. Beta blockers dose is less than that for CVD --- etc.
- 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:

unknown MOA

- 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: may be used, but Betablockers + anti seizures are used more

- **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.**
- **The beneficial effects of valproate may be due to:**

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.