pharmacology
Team 438

MED438
KING SAUD UNIVERSITY

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Neuropsychiatry Block

Pharmacology Team 438

Drugs Used in Headache And Migraine

Objectives

By the end of the lecture , you should know:

- Differentiate between types of headache regarding their symptoms, signs and pathophysiology.
- Recognize drugs used to prevent migraine.
- Identify drugs used to rescue and abort migraine.
- Elaborate on the pharmacokinetics, dynamic and toxic profile of some of these drugs.

Color index:

Black : Main content
Red : Important
Blue: Males' slides only
Pink : Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Editing File

1 Headache

Pain anywhere in the region of the head or neck.

• It is caused by disturbance of the Pain-Sensitive Structures around the brain:

1) **Within the cranium:** blood vessels, meninges, & cranial nerves.
2) **Outside the cranium:** muscles, nerves, arteries, veins, subcutaneous tissues, eyes, ears, and other tissues.

2 Migraine

Recurrent attacks of throbbing headache, unilateral [1] or on both sides.

• Lasting from > 2 up to 72 hrs.
• Preceded (or accompanied) by **AURA.**
• pain is usually on **one side** of head with facial and neck pain, nausea and vomiting.

Types of Migraine:

Common: Without aura (80%)

Classic: With aura (20%)

★ **Aura:** Perceptual disturbance of motor **< sensory nature.**

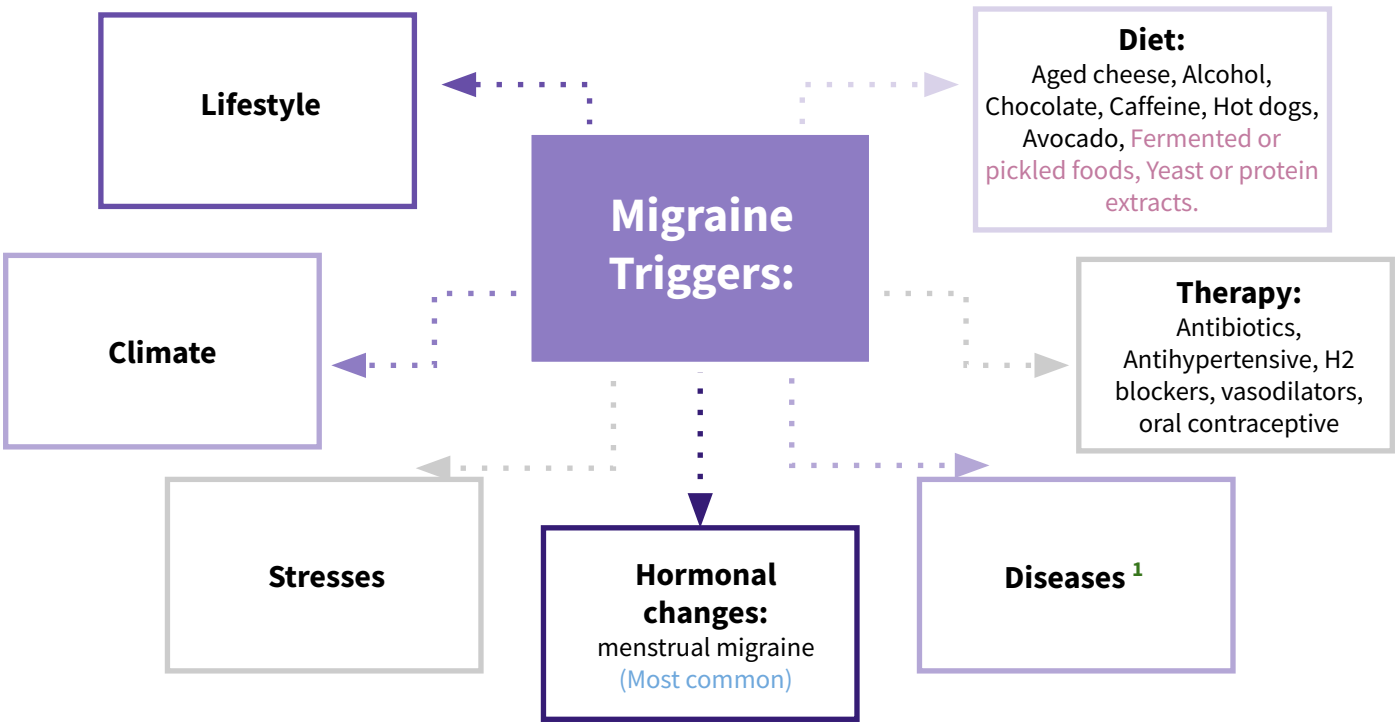
- **Visual**: Photophobia (↑ sensitivity to light)
- **Auditory**: Phonophobia (↑ sensitivity to sound)
- **Olfactory** unpleasant smell.
- **Sensory** abnormal sensation of at face, extremities.

-Develops over 5-20 min & last fewer than 60 min.

Phases of Migraine

1) Pro-drom phase	• A change in mood or behavior (irritability, neck stiffness) that starts hours or days before headache. • It is experienced by 60% of migraineurs
2) Aura-phase	• **Sensory** > motor symptoms starts 5-20 min before the migraine attack. It is experienced by 20% of migraineurs.
3) Headache phase	• Moderate to severe pain,↑ with activity + anorexia, vomiting. • **Intolerance to light**, sounds, odors • Blurry vision, Blocked nose, Pale face, Sensations of heat or coldness, Sweating, & Tenderness of the scalp.
4) Post-drom phase	• Still not normal. More likely fatigue → irritability, impaired concentration, scalp tenderness, mood changes, & GIT symptoms.

1. One part of the head



Migraine Causal Theories

1 Vascular

2 Cortical Spreading Depression

3 Dopaminergic Hypersensitivity

Triggers → Intracranial vasoconstriction → migraine aura → focal ischemia → ↑inflammatory mediators → rebound vasodilation → ↑ permeability & leak → inflammatory reaction → activates perivascular **nociceptive** nerves → It throbs as blood flow at these sensitive area with each heartbeat → migraine headache.

4 Neurovascular theory

5 Mediators [Serotonin]

Triggers → Release K / glutamates → Creates a slowly well-defined depolarizing wave → depolarize adjacent tissues → propagating at a rate of 2-6 mm/min → vasoconstriction→ migraine aura→**activate trigemino-vascular complex**→**vasodilation** → migraine headache.

Stimulation of the trigeminal nerve causes the release of **vasoactive peptides**(e.g calcitonin , substance P ,neurokinin A) this is responsible for the head pain, as well as the facial and neck pain, experienced during migraine.

1. CNS diseases, destruction or dysfunction diseases.

Treatment Strategy

- They reduce the recurrence frequency, severity, duration & / or disability.
- increase responsiveness to abortive therapy.

N.B. Full effect of therapy needs several weeks to manifest & should continue for 6 m. & can be repeated.

A) Anti-epileptics:

Block Na+ channel & augment GABA at GABA-A receptors
e.g **Topiramate, Valproic**

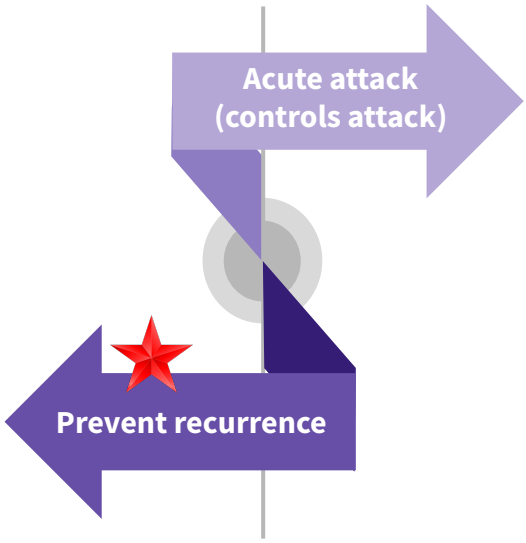
B) Antidepressants:

TCA; **amitryptylin** and **nortryptyline**

C) Antihypertensives:

- B-blockers; **propranolol**[1]

Propranolol is commonly used in **prophylaxis** of migraine attack.



A) ABORTIVE therapy

(For severe- disabling pain)

- They **specifically target pathways of migraine** by reducing meningeal dilatation & reduces neural activation via 5HT1 agonism i.e stopping headache as it its evolving.
- Abortive medication **effective if taken early,just before the pain starts**, losing effectiveness once the attack has begun.

So they must be rapidly acting.

B) RESCUE therapy [2]

(For mild to moderate pain)

- **Non-specifically**
- Target individual **symptoms**. i.e. Alleviating Pain, emesis and associated symptoms.

Acute Attack

Rescue Therapy

Class	Analgesic	Antiemetics
Drugs	**1- NSAIDs:** • **Acetaminophen** • **Aspirin** (weaker) • **Ibuprofen**, **Naproxen** → for **mild to moderate** attack with **no** nausea & vomiting.	**1- Dopamine Antagonists** • **Domperidone**[4] **Increases the Gastro-prokinetic:** ↑ Absorption[5] & bioavailability of abortive therapy. • **Phenothiazines** (**Promethazine**): Has a **sedative** effect.
	2- Non-opioid [3] μ (mu) agonist • **tramadol** (Tramadol also inhibits serotonin reuptake)	**2- 5HT3 antagonists**(for Chemotherapy) • **Ondanseteron , Granisetron:** For severe nausea and vomiting.
		3- H1 antagonist(not for drivers) • **Meclizine, diphenhydramine:** Has anti-histaminic+ sedative + Anti-cholinergic effects.

1- Gold standard
2- it not to treat the migraine, only for signs and symptoms.
3- when pain is severe
4- Migraine inhibit gastric emptying
5- by increase GIT motility

Acute Attack

Abortive Therapy : a) Ergots

Drugs	Ergotamine tartarate rare clinical use due to severe adverse effects,restricted use	Dihydroergotamine (DHE) preferred in clinical setting
MOA	• Product of Claviceps purpurea; a fungus growing on rye/grains ★ **Non-Selective** [1] ★ **Partial agonism at 5HT1 receptors** (5HT-1D/1B found in cerebral And meningeal vessels)**:** ○ ↓ release of vasodilating peptides ○ ↓ excessive firing of nerve endings ○ At blood vessels → ↓ vasodilation & stretching of the pain endings • **Partial agonist effect on α-adrenoceptors** → vasoconstriction (peripherally, not desirable)	
P.K	• Oral absorption incomplete (erratic) + slow → low bioavailability. • Can be taken orally (**Cafergot** [2] is a formula which contains caffeine and ergotamine) , sublingually, rectal suppository, inhaler. • Despite T1/2 nearly 2 hours, **ergotamine** produces vasoconstriction → **24 hours** or longer due to high and long tissue binding ability. • **Ergotamine tartrate** has **significant side effects**, and may worsen the nausea and vomiting associated with migraine.	• Nasal spray, inhaler & **injectable forms** (good to use if patient is **vomiting**) • Given parenterally, and eliminated more rapidly than **ergotamine**, presumably due to its rapid hepatic clearance and has less adverse effects.
Uses	★ They are only used to abort the attacks (Except **Dihydroergotamine** [3] can be given for severe, recurrent attacks **not** responding to other drugs) • Their use is restricted to patients with frequent, moderate attack or infrequent but severe attacks.	
ADRs	• GI upset • Feeling of cold and numbness of limbs, tingling [4] ★ Anginal pain [4] due to **coronary spasm**, and disturbed cardiac rhythm (tachycardia or bradycardia) ★ Prolong use → **rebound headache due to vasodilation** followed by **Vasoconstriction**. • Prolong use and high dose → paraesthesia (tingling or burning sensation)	
C.I	• Pregnancy; fetal distress and miscarriage (ergot is uterine stimulant and vasoconstrictor) • Peripheral and coronary vascular diseases • Hypertension • prophylaxis of migraine • Liver and kidney diseases [5] • In concurrent use with **triptans** (given at least 6 hrs from last dose of triptans **or** 24 hrs from stopping ergotamine and B-blockers) [6]	

1. Non selective means that it act on many receptors such as : dopamine , alpha 1 and alpha 2 and serotonin receptors
2. This combination to improve sign and symptoms
3. We don't start with DHE , only use it when patient Not responding to other drugs
4. Due to vasoconstriction
5. Because they have ability to bind to tissue , so they stay in the body long time → their metabolism becomes longer
6. With B- blockers will cause reflex tachycardia

Acute Attack

Abortive Therapy : b) Triptanes

Drugs	Sumatriptan[1]	Zolmitriptan	Naratriptan
MOA	• **Selective** Agonism at 5-HT1 (5-HT1D/1B) receptors • Similar to ergotamine except that triptans are more selective as serotonergic agonist. ★ **No α1, α2, β –adrenergic, dopamine or muscarinic receptors.** • Triptans inhibit the release of vasoactive peptides, promote vasoconstriction, and block pain pathways in the brainstem. • Triptans inhibit transmission in the trigeminal nucleus caudalis		
P.K	**Bioavailability:** • Oral → low • **Subcutaneous → 97%, peaks after 2 min** & T1/2 nearly 2 hours (fast action with SC, good for patient with **vomiting**) • **Given oral, nasal spray, and injectable**	• **Oral** bioavailability **40**%, peaks after 2 hrs & T1/2 nearly 3 hours. • **Given nasal spray, and injectable**	• **Oral** bioavailability **70**%, peaks after 2 hrs & T1/2 nearly 6 hours (slower onset,**less side effects**) • **Given Oral preparations**
Uses	• To abort attacks in patients with frequent, moderate or infrequent but **severe attacks.** • In **cluster headache** " extremely painful migraine "		
ADRs	• Most of ADRs are the same as with ergot but **triptans** are **better tolerated**.[2] • Mild pain and burning sensation at the site of injection. • Vasospasm, Ischemic heart; Angina and Arrhythmias ★ **Zolmitriptan[3]: Chest & neck tightness, Coronary vasospasm & Somnolence**		
C.I	• History of ischemia • Cerebrovascular disorders[4] • Peripheral vasospastic diseases • Uncontrolled hypertension ★ In concurrent use with ergots or others **inducing vasospasm** ★ In concurrent use with MAOIs, lithium, SSRIs, → (5HT increased to toxic level) • Renal or hepatic impairment		

1- for emergency, part of rescue
2- less side effects
3- due its longer action
4- carotid aneurysm , stroke

Deciding whether better with a triptans or with DHE

If the patient:

Has migraines a day or less and need rapid relief:	Pregnant woman	With headache episodes lasting 2 or 3 days
Triptans are often a better choice	**paracetamol** or **intranasal**[1] **sumatriptan** and or **diphenhydramine**, **meclizine** are **safe**.	**DHE is often the optimal choice** because it has longer **T1\2**

- The **form** of drug preparation could influence the choice
- **Injectable Sumatriptan** reaches Tmax the fastest followed by DHE nasal spray and Rizatriptan.

Factors When Choosing a Triptans:

Drug	T max	T1\2
DHE	1	10
Sumatriptan SQ	0.25	2
Rizatriptan	1-1.5	2-3
Zolmitriptan	2.5	3
Naratriptan	2-3	6
Eletriptan	2.8	4
Frovatriptan	2-3	26

- **Differences** in the time to peak blood concentration **Tmax,** equates with faster relief of pain.
- **Differences** in **t1/2** → a clinical effect in terms of **recurrence** of headache.

★ For **extremely fast relief within 15 min**. **injectable Sumatriptan** is the **only choice**.

★ If expected **re-dosing is needed** & / or **recurrence of headache** →**Naratriptan**, **frovatriptan**, have slower onset, fewer side effects, and a lower recurrence rate.

★ **Menstrual migraine: Frovatriptan** (longer T1\2= 26hrs) 2.5 mg twice per day beginning two days before the anticipated onset of menstrual migraine and continuing for six days.

1- to not expose the patients to high doses, also it will reach CNS without reaching to the fetus.

Quiz

MCQ

1- Which of the following drugs for headache is contraindicated in patients with peripheral vascular disease?

A- Ergotamine B- Aspirin C- Naproxen D- Ibuprofen

2-A patient with a moderate headache with no nausea or vomiting which drug would you prescribe?

A- Zolmitriptan B- Ergottartarate C- Amitriptyline D- Naproxen

3-Which of the following drugs causes rebound headaches with prolonged use?

A- Dihydroergotamine B- Propranolol C- Aspirin D- Sumatriptan

4-Which of the following drugs acts as a central analgesic?

A- Propranolol B- Aspirin C- Tramadol D- Ibuprofen

SAQ

-A 26-years-old pregnant female came to the ER suffering from migraine for less a day, she said that she can't handle the pain more and asked for a rapid relief drug.

1-Which drug would be the most appropriate in this situation?

2-What is the mechanism of action of that drug?

3-List other drugs that are safe for pregnant women having migraine.

-Nasser is 31-years-old male came to the ER with a history of recurrent severe headache attacks for 2 days and he mentioned that he took paracetamol two times but it wasn't helpful.

4-Which drug would be the most appropriate to this patient ?

5-Mention 3 ADR of this drug,

Answers:

MCQ

Q1	A
Q2	D
Q3	A
Q4	C

SAQ

Q1	sumatriptan
Q2	Selective Agonist at 5-HT1 (5-HT1D/1B) receptors
Q3	paracetamol, diphenhydramine, meclizine
Q4	Dihydroergotamine (DHE)
Q5	Anginal pain & disturbed cardiac rhythm - Rebound headache(Prolong use) - Paraesthesia(Prolong & high dose)

pharmacology

Team 438

Good Luck , Future Doctors!

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Share with us your ideas !