MED437
KING SAUD UNIVERSITY

Pharmacology
435 team

Pharmacology
Team 437

Drugs Used in Headache and Migraine

Objectives:

- 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:

- Drugs names
- Doctors notes
- Important
- Extra

Editing File

To Understand Better

Headache	Migraine
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.) (intracranial) **2. Outside the cranium:** (muscles, nerves, arteries, veins, subcutaneous tissues, eyes, ears and other tissues.) (extracranial)	-Recurrent attacks of throbbing headache, unilateral or on both sides. -Lasting from > 2 up to 72 hrs. + preceded (or accompanied) by **AURA** abnormal felling **.** **-Aura:** seeing flashes of light, blind spots or feeling tingling in arm. -pain is usually on **one side** of head with facial and neck pain and nausea and vomiting. -Curtain like effect over one eye

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.

Types of migraine:

1- **Common** (without aura 80%.)

2- **Classis** (with aura 20%.)

داء الشقيقة متلازمة لها أعراض كثيرة لكن الصداع هو أشهرها ولا نقارنها بالصداع العادي لشدته **المحاضرة تركيزها الأساسي على علاج الصداع الناتج من الشقيقة**

So headache ≠ migraine, headache is a symptom of migraine

Phases of Migraine: (self reading)

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 increase anorexia, vomiting & anorexia • **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, either; More likely fatigued → irritability, impaired concentration, scalp tenderness, moodchanges, GIT symptoms,

Migraine Triggers:

Diet	• **Aged cheese** (contains **tyramine** → constrict blood vessels → hypertension), Alcohol, Chocolate, Caffeine in high dose, Hot dogs, Avocado, Fermented or pickled foods, Yeast or protein extracts, Aspartame.
Therapy	Antibiotics, Antihypertensive, H_2 blockers, Vasodilators, Oral contraceptives.
Diseases	(e.g. hypertension).
Hormonal changes	Menstrual migraine (Most common) Because estrogen is neuroprotective & its declining during menstrual cycle.

Stresses, Climate & Lifestyle.

Migraine Causal Theories

Vascular, Cortical Spreading Depression, Neurovascular theory, Mediators [Serotonin], Dopaminergic Hypersensitivity.

Vascular theory:

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

Triggers → Release K / glutamates (too much excitation) → (Neurovascular theory)Creates a slowly well-defined depolarizing wave → (Mediators Serotonin) depolarize adjacent tissues → propagating at a rate of 2-6 mm/min → vasoconstriction → migraine aura→ (Dopaminergic Hypersensitivity)activate trigemino-vascular complex →**vasodilation** → migraine headache

Stimulation of the trigeminal nerve causes the release of **vasoactive peptides**; this is responsible for the head pain, as well as the facial and neck pain, experienced during migraine.

Treatment Strategy

Prevent recurrence prophylactic

-Reduce recurrence frequency severity duration & / or disability
-increase responsiveness to abortive therapy.
(drugs stops migraine)
N.B. Full effect of therapy needs several weeks to manifest & should continue for 6 m. & can be repeated.

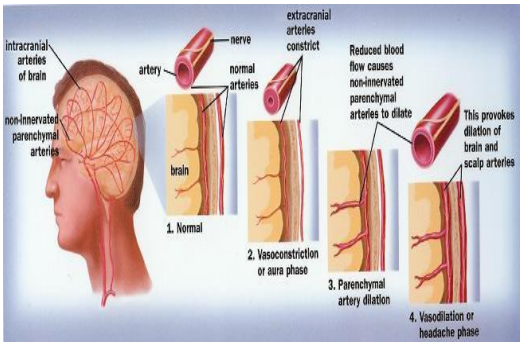
Acute attack (Controls attack)

ABORTIVE therapy (severe-disabling)
Treat the **cause** **stop attack**

They specifically target pathways of migraine by reducing meningeal dilatation & reduces neural activation via 5HT1 agonist (serotonin constrict blood vessels) i.e stopping headache as it its evolving
- Abortive medication **effective if taken early,just before the pain start**s(before vasodilation) ,losing effectiveness once the attack has begun (may prevent further attacks only)
So they must be rapidly acting.

RESCUE therapy (mild to moderate)
Treat **Symptoms**

Non-specifically target individual symptoms. i.e. Alleviating Pain emesis and associated symptoms



الفكرة كلها ان الجسم اذا ضاقت الأوعية الداخلية للمخ ينخرش ويحاول يوسعها بسرعة فلما تتوسع تخرج السوائل وترفع الضغط الداخلي، فتقسيم الأدوية يعتمد هل هي راح تعالج السبب)التوسع (ولا الأعراض)الصداع والغثيان(

Step 1 USMLE Tutorial - All About Headaches
This video summarizes the whole lecture in a simple way

PREVENT RECURRENCE

Anti-epileptics

Block Na^+ channel & augment GABA at GABA-A receptors **Topiramate**, **Valproic** we can't use phenytoin it is toxic

Antidepressants

TCA; **amitryptylin** and **nortryptyline.**
Why TCA? Bc they have 5-HT & H1 actions, which are good for migraine

Antihypertensives

B-blockers; **propranolol**
Ca^{2+} Channel Blockers
Propranolol is commonly used in **prophylaxis** of migraine attack.

Acute attack (RESCUE THERAPY)

Drug	Analgesics	Anti-emetics (prevent nausea and vomiting)
Mech. of action	1- **NSAIDs:** • **Acetaminophen** • **Aspirin** (weaker) • **Ibuprofen**, **Naproxen** → (Drug of choice) for **mild to moderate** attack with **no** nausea & vomiting. 2- **Narcotic analgesic (μ agonist): tramadol** = (central analgesic) → causes tolerance. -Tramadol also inhibits serotonin reuptake	**1- Dopamine Antagonists** A- **Domperidone** • **Gastro-prokinetic effect** (gastric empting) (increase gastric motility → Increase absorption of drug & reduce vomiting) → ↑ Absorption & bioavailability of abortive therapy. B- **Phenothiazines** (**Promethazine**): Has a **sedative** effect. **2- 5HT3 antagonists** **Ondanseteron**, **Granisetron**:(the best drugs for vomiting) For severe **nausea** and **vomiting**. **3- H1 antagonist** **Meclizine**, **diphenhydramine**: Has **anti-histaminic** + **sedative** + **Anti-cholinergic** effect. → Safe for pregnancy.

7:55 min

ACUTE ATTACK (ABORTIVE THERPY)

1- Ergots

Drug	Ergotamine tartarate (rare clinical use due to sever adverse effects) (resticted use)	Dihydroergotamine (DHE) (preferred in clinical setting)
Mech. of action	- Product of Claviceps purpurea; a fungus growing on rye/grains - **Non-Selective** - **Partial agonism at 5HT1** (5HT-1D/1B found in cerebral And meningeal vessels) **receptors.** → - ↓ release of vasodilating peptides - ↓ excessive firing of nerve endings - At blood vessels → ↓ vasodilation & stretching of the pain endings - **Partial agonist effect on a-adrenoceptors** → vasoconstriction good for hypotensive patient	
P.K	- Oral absorption (as **Cafergot from caffeine)** - Incomplete (erratic) + slow → low bioavailability. - $T_{1/2}$ nearly **2 hours**, ergotamine produces vasoconstriction → **24 hours** or longer due to high and long **tissue binding ability.** - Can be taken sublingually, rectal suppository, inhaler. - **Ergotamine tartrate** -Reserve drug- 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. * Better than Ergotamine tartarate bc of the P.K characteristics. * has an efficacy similar to that of sumatriptan, but nausea is a common adverse effect.
Indications	- They are only used to abort the attacks (Except **Dihydroergotamine** 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	• GIT upset • Feeling of cold and numbness of limbs, tingling • Anginal pain due to **coronary spasm**, and disturbed cardiac rhythm (tachycardia or bradycardia) therefore its not safe for heart problem patients • 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 • Liver and kidney diseases • **prophylaxis of migraine**. because they have the same mechanism • In concurrent use with **triptans** (at least 6 hrs from last dose of triptans or 24 hrs from stopping ergotamine and β-blockers)	

ACUTE ATTACK (ABORTIVE THERAPY) Cont.

2- **Triptanes**

- **Selective** Agonist at 5-HT_1 (5-HT1D/1B) receptors. → better than ergots.
- Similar to **ergotamine** except that **triptans** are more **selective** as **serotonergic agonist**.
- **No a1, a2, β –adrenergic, dopamine or muscarinic receptors.**

All theses drugs are important to know it well, especially P.K

Drug	**Sumatriptan** Super fast.	**Zolmitriptan**	**Naratriptan**
	oral, nasal spray, and injectable	nasal spray, and injectable	Oral preparations
MOA	**- 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 & $T_{1/2}$ nearly 2 hours (fast action with SC, subcutaneous, good for patient with **vomiting**)	**Oral** bioavailability **40%**, peaks after 2 hrs & $T_{1/2}$ nearly 3 hours.	**Oral** bioavailability **70%**, peaks after 2 hrs & $T_{1/2}$ nearly 6 hours (slower onset, **less side effects**)
Indications	• To abort attacks in patients with frequent, moderate or infrequent but **severe attacks**. • In **cluster headache** "Severe headache or pain mostly around the eyes' • Sumatriptan → first-line therapy for acute severe migraine attacks		
ADRs	• Most of adv are the same as with ergot but **triptans** are **better tolerated**. • Mild pain and burning sensation at the site of injection. • Vasospasm, Ischemic heart; Angina and Arrhythmias **Zolmitriptan: Chest & neck tightness, Coronary vasospasm & Somnolence** Sleepless +drowsiness		
C.I	• Peripheral vasospastic diseases • Uncontrolled hypertension • History of ischemia • Cerebrovascular disorders • 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.		

Deciding whether better with a triyptan or with DHE

Patients:

- migraines a day or less and need rapid relief → **Triptans** (they give rapid relief)
- pregnant women → **paracetamol** or intranasal **sumitriptan** and or **diphenhydramin**, **meclizine** are **safe**.
- Patients with headache episodes lasting 2 or 3 days → **DHE** because it has longer $T_{1\backslash 2}$

- The **form** of drug preparation could influence the choice,
- **Injectable Sumatriptan** reaches T_{max} the **fastest** followed by **DHE nasal spray** and **Rizatriptan.**

Factors when Choosing a Triptans:

Medication	T_{max} (h) Give rapped effect	$T_{1\backslash 2}$ (h) Reduce pain and prevent recurrence for longer time
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 T_{max}, equates with faster relief of pain.
- **Differences** in $t_{1/2}$ → 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.
- Menstraul migraine: **Frovatriptan** (longer $T_{1\backslash 2}$= 26hrs) 2.5 mg twice per day beginning two days before the anticipated onset of menstrual migraine and continuing for six days.

Summary

ACUTE ATTACK: A- Rescue therapy (to treat the symptoms)

	Analgesics		Antiemetics used with analgesics in case of pain+vomiting			
Group	NSAIDs	Opioid	Dopamine Antagonists	Phenothiazines	5HT3 antagonists	H1 antagonist
Drug	Aspirin - Acetaminophen **(Paracetamol safe with Pregnancy)** ibuprofen, naproxen	Tramadol	Domperidone	Promethazine	Ondanseteron Granisetron	Meclizine diphenhydramine **(safe with Pregnancy)**
Note	Use alone in case of mild to moderate pain with no vomiting or nausea	μ agonist	Gastro-prokinetic: ↑ Absorption, bioavailability of abortive therapy	Dopamine antagonists Sedation (antipsychotic)	for severe nausea & vomiting	●Antihistamine ●sedation ●Anticholinergic

Acute Attack: B- abortive therapy

Group	Ergots (only in SEVERE cases)		Triprans		
Drug	**Ergotamine tartarate** (restricted use)	**Dihydroergotamine (DHE)** (preferred)	**Sumatriptan (safe with Pregnancy)**	**Zolmitriptan**	**Naratriptan**
M.O.A	Partial agonism at 5HT1 receptors (5HT-1D/1B found in cerebereal & menigeal vessels) **(non-selective)**		5HT1 agonists **(selective)** No α1, α2, β –adrenergic , dopamine or muscarinic receptors.		
P.D	●↓release of vasodilating peptides ●↓excessive firing of nerve endings ●effect on α-adrenoceptors → vasoconstriction		inhibit the release of vasoactive peptides, vasoconstriction, block pain pathways in the brainstem. inhibit transmission in the trigeminal nucleus caudalis		
P.K	●erratic oral absorption → low bioavailability. ●high & long tissue binding ability: vasoconstriction effect last for long time. ●has significant S.E.	●Eliminated rapidly, due to its rapid hepatic clearance & less S.E ●injectable (good to in of vomiting) (antiemetic)	Bioavailability: -Oral low -SC 97%, **(for fast relief - 15min- fast action with SC**, good for patient with vomiting)	Oral bioavailability 40%	Oral bioavailability 70%, peaks after 2 hrs (slower onset, less side effects).
Uses	**●DHE can be given for severe, recurrent attacks not responding to other drugs and lasting 2-3 days.**		●Patient with migraines for a day or less and need rapid relief. ●In cluster headache.		
S.E	●GIT upset ●Cold & numbness of limbs ●Anginal pain & disturbed cardiac rhythm ●Rebound headache (Prolong use) ● Paraesthesia(Prolong & high dose)		●Same as with ergot but triptans are better tolerated. ●Mild pain & burning sensation at the site of injection. ●Vasospasm, Ischemic heart, Angina & Arrhythmias. **Zolmitriptan:** Chest & neck tightness - Coronary vasospasm - Somnolence		
C.I	●Pregnancy → miscarriage ●Hypertension. ●Liver & kidney diseases ●Prophylaxis of migraine ●Peripheral and coronary diseases. ●With Triptans		●Peripheral vasospastic diseases ●uncontrolled hypertension ●History of ischemia ●cerebrovascular disorders ●with ergots or others inducing vasospasm ●with MAOIs, lithium, SSRIs → (5HT increased to toxic level)		

Questions

MCQs

1. Is the following statement true or false, Ergots are more selective than triptanes.

A) True
B) False

2. A pregnant woman is experiencing a mild headache with no nausea or vomiting what is the drug of choice?

A) Sumatriptan
B) Meclizine
C) Ergot tartarate
D) Domperidone

3. Which of the following has the fastest onset of action?

A) Rizatriptan
B) Frovatriptan
C) Sumatriptan
D) Meclizine

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

A) Ergot tartarate
B) Zolmitriptan
C) Amitriptyline
D) Naproxen

5. Which of the following drugs causes rebound headaches with prolonged use?

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

MCQs answers:

1) B
2) B
3) C
4) D
5) A

Questions

MCQs

6. Which of the following drugs acts as a central analgesic?

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

7. A taxi driver is complaining of nausea what should we prescribe him?

A) Domperidone
B) Ergots
C) Sumatriptan
D) Aspirin

8. What is the MOA of ergots?

A) Increase firing rates of nerve impulses
B) Decrease firing rates of nerve impulses
C) Increase release of vasodilators
D) Decrease release of vasoconstrictors

MCQs answers:
6) C
7) A
8) B

SAQ

1.Explain when Dihydroergots should be prescribed and used.
Dihydroergotamine can be given for severe, recurrent attacks not responding to other drugs.

2.List the preventive drugs and an example of each.

1. Anti-spastic: Tizanidine
2. Antidepressants: nortytrptan
3. Antiepileptic: topiramate
4. Anti-hypertensive: propranolol

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References:

- Doctors' slides and notes.
- Pharmacology Team 435.

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