PHARMACOLOGY TEAM

Lecture : 6

# Drugs used in headache & Migraine

Done by: Shahd Al-Awwad & Sara Al-Abdualqader

Revised by: Abdullah AL-Anazi

# 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.

**Headache:** pain in any region of the head & neck.

It is caused by disturbance of the

Pain – Sensitive Structures around the brain

It can be a symptom of a number of different conditions of the head or neck or any where in the body or a referred pain.

Within the cranium :

( blood vessels, meninges, cranial nerves)

Outside the cranium:

(the periosteum of the skull, muscles, nerves , arteries ,veins, subcutaneous tissues ,eyes, ears and other tissues)

# Classification of headache

**Secondary: Based on the etiology**

**Trauma**: of head or neck

**Vascular disorders:** ischeamic stroke, intracrainial hemorrhage.

**Disease:** intracranial tumors,infection,

**Homeostasis disorders:** high BP, fastening(drop in the blood glucose level), hypothroidsm.

**Others……**

**Treatment:**

Treat the etiology

**Primary:**

**Migraine(most common),** tension type headache, cluster headache, trigeminal cephalgias and others where cause in unknown

**Treatment by:**

In most:
NSAIDs(analgesics)

**If severe: Tramadol " mildest one of Opoids"**

# Migraine

- Recurrent attacks of throbbing(pulsatile) headache
- Unilateral / or on both sides
- Lasting from 2 up to 72 hrs.
- Preceded *(or accompanied)* by AURA

For Example:
In Aura or During the attack phase When it's induce Vomiting, the reason behind it is: During Vasodilatation it triggers the Chemo receptors & Induce vomiting

**Perceptual disturbance of motor < sensory nature**

**"He'll FEEL that he is going to have migraine BEFORE the migraine attack through 1 of the 3 sensations "**

- visual [ Photophobia (↑sensitivity to light) ]
- auditory [ Phonophobia (↑ sensitivity to sound) ]
- olfactory unpleasant smell

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

# Migraine

**1.Prodrom Phase;** a change in mood or behavior 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. Postdrom Phase:** still not normal, either;

* More likely fatigued → irritability /impaired concentration /scalp tenderness /mood changes / GIT symptoms, ……

* Less likely refreshed, hyperactive, apprehensive….

# Migraine

- Types of Migraine:
  - COMMEN : Without Aura [80%]
  - CLASSIC: With Aura [20%]
- Triggers:

**Diet:**

Aged cheese, Alcohol, Chocolate, Caffeine, Hot dogs, Luncheon meats, Avocado, Fermented or pickled foods, Yeast or protein extracts, Onions Nuts,

**Therapy**

Antibiotics, Antihypertensives, $H_2$ blockers, Vasodilators, Oral contraceptives

**Stresses**

**Hormonal changes**

Ex: menestral period

**Climate**

**Diseases**

**Life Style**

Ex:travelling(jet lag)

# Migraine

## Migraine causal Theories:

### 1-Vascular

Triggers⟶ Intracranial vasoconstriction ⟶ migraine aura ⟶ focal ischemia ⟶ ↑ mediators ⟶ rebound vasodilatation ⟶ ↑ permeability & leak ⟶ inflammatory reaction ⟶ activates perivascular nociceptive nerves ⟶ migraine headache⟶ It throbs as blood flow at these sensitive area with each heart beat

Glutamate is excitatory neurotransmitter

### 2-Cortical Spreading Depression (Depolarization usually from occipital to Frontal lobe)

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⟶ Along its spread $H^+$ and $K^+$ ions diffuse to the pia matter ⟶ activate C-fiber meningeal nociceptors ⟶release proinflammatory soup of neurochemicals (CGRP, SP, ….) ⟶ activate trigeminovascular complex ⟶ vasodilation ⟶ migraine headache

### 3-Mediators "Serotonin"

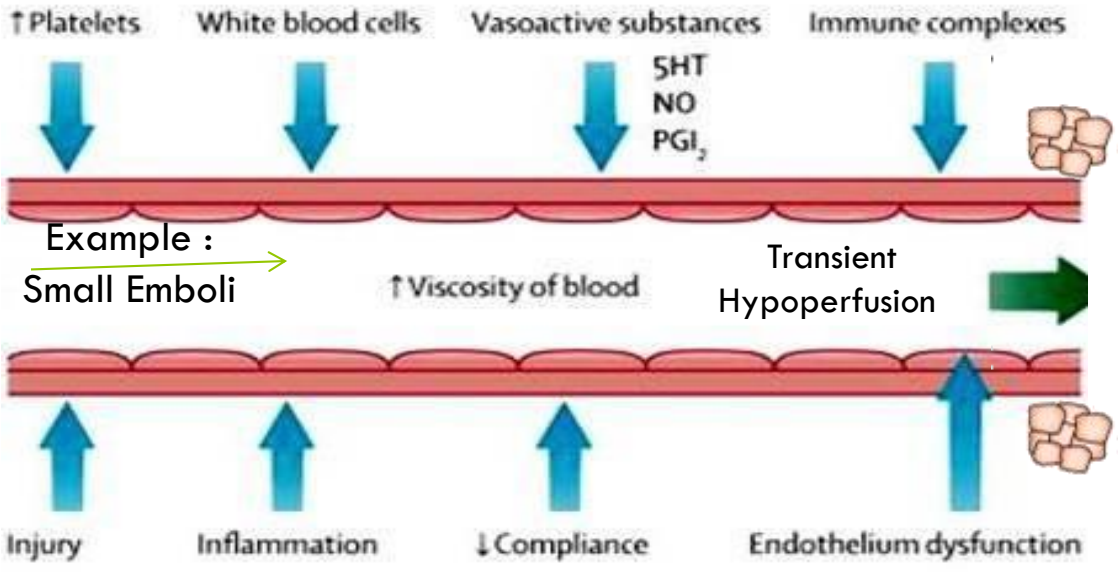
Serotonin ⟶ Vasoconstriction⟶ Body release inflammatory cells " because the body consider the constriction as a little of ischemia " ⟶Vasodilatation ⟶Headache

# Migraine

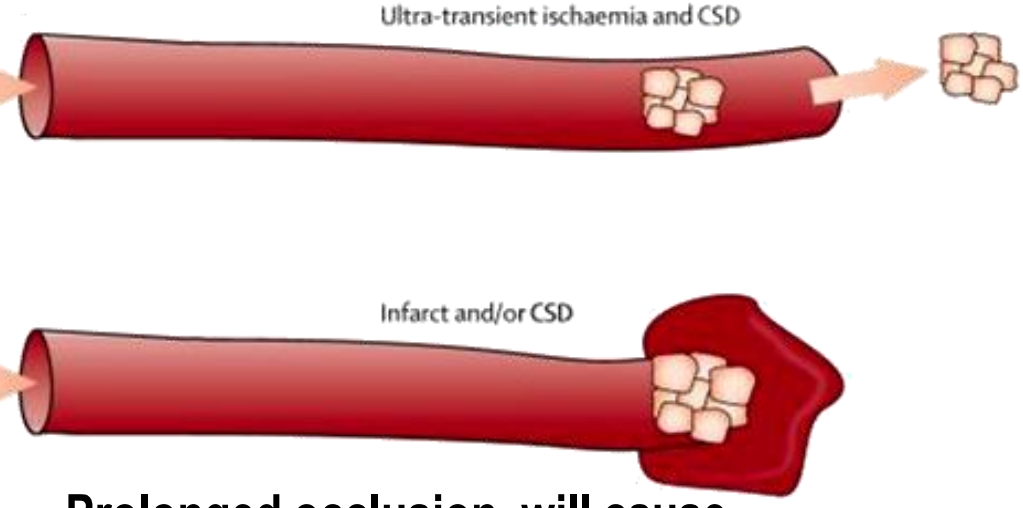
## Other theories :

- Neurovascular
- Immunological
- Dopamenergic Hypersensitivity
- Magnesium Deficiency

**To clarify the main concept of migraine causes theories :**




**Transiently occlude to initiate CSD**




**Prolonged occlusion will cause tissue microinfarction**



Slides | Important | Doctor's Notes | Explanation

# Migraine

## Treatment Strategies

### A-Acute Attack

As a Doctor Your aim is :

to control the attack

**1-RESCUE THERAPY (Mild-Moderate):**

Non-specifically target individual symptoms , i.e. alleviating (Reduce)

pain, emesis and associated symptoms

Mainly treat the Symptoms

**2-Abortive Therapy (Severe- Disable):**

They specifically target pathways of migraine by ↓ meningeal dilatation & ↓ neural activation via $5HT_1$ ( Manengies: the most area that have Serotonin Receptors ) agonist (since the serotonin action : vasoconstriction → i.e. stopping headache as it is evolving.

Abortive medications > effective if taken early, losing effectiveness once the attack has begun

So they must be rapidly acting

Treatment by giving : Abortive & Rescue Therapy in severe cases

### B-Prevent Recurrence:

As a Doctor your aim is to:

↓recurrence frequency, severity, duration & / or disability

↑responsiveness to abortive therapy

**N.B.** *Full effect of therapy needs several weeks to manifest*

*& should continue for 6 m.*

*& can be repeated*

# A- Acute attack

## 1- rescue therapy

| | |
|---|---|
| • analgesic | •NSAIDs / Aspirin< Acetaminophen<br>•Mild-opioid: μ agonist; tramadol act on 5HT & NE receptors<br>•Sedatives |
| •Antiemetic | •Dopamine Antagonists (Domperidone) → it has gastro-prokinetic effect (it empties the stomach so it'll reduce nausea & vomiting) and increase Absorption & bioavailability of abortive therapy. (doesn't cross BBB & no sedation effect.)<br>•Phenothiazines (Promethazine) → dopamine antagonist and it has sedating effect. " as side effect" so, we chose Promethazine is better in vertigo<br>•5HT3 antagonists (Ondanseteron - Granisetron ) → rarely giving for migraine (in severe cases with severe vomiting only). It is only used as a potent antiemetic in two condition :<br>1) cancerous patients with chemotherapy<br>2) vomiting following an abdominal surgery<br>•H1- antagonist ( Meclizine) → anti-histamine & anti-cholenergic " last choice" |
| Others | Steroids " because part of migraine has inflammation, steroids will be useful"<br>It has anti-inflammatory action. |

## 2- abortive therapy

By acting on 5HT1

- agonist (selective) → Triptans
- Partial agonist (non-selective) → ERGOTS

Acts on "5HT2, dopamine, α adrenergic receptors" – " it's non selective so we expect side effects may occur, & it's good in migraine because it triggers $\alpha_1$ + $\alpha_2$ receptors + 5HT1 "

- CGRP Antagonist

calcitonin gene-related peptide (CGRP)

this class of medications will be useful to treat migraines.

# Ergots

Product of Claviceps purpurea; a fungs growing on rye & other grains. It causes gangrene and abortion if giving in high doses, Non-selective

| | |
|---|---|
| Agonist at 5HT1 receptors | •At presynaptic trigeminal nerve endings (carrying pain signals to the brain):<br>Decrease release of vasodilating peptides<br>Decrease excessive firing of these nerve endings |
| | At blood vessels:<br>Decrease vasodilation & stretching of the pain endings<br>Decrease transmitter release in the perivascular space |
| Partial agonist effect on α-adrenoceptors | Vasoconstriction |
| Antagonist to some dopaminergic & serotonergic receptors | |

# Ergots

## Ergotamine tartarate

- Oral, sublingual, rectal suppository (not favorable by the patients), inhaler & injectable forms
- Oral preparation is slow so once we add caffeine the absorption will increase (cafegrot)
- Oral absorption: Incomplete (erratic) + slow → low bioavailability
- Sublingual: Low bioavailability
- Rectal suppository: Better bioavailability
- Elimination : Extensive hepatic 1st pass metabolism
- Excretion: 90% of metabolites in bile Traces unmetabolized → in urine and feces
- Despite t1/2 nearly 2 hours, ergotamine produces vasoconstriction → 24 hours or longer due to high and long tissue binding ability.

## Dihydroergotamine

- Nasal spray, inhaler & injectable forms
- Rapid but short acting, but still longer than Ergotamine
- Dihydroergotamine is eliminated more rapidly than ergotamine, presumably due to its rapid hepatic clearance

*Preparation is very important, because the varying of speed of action..

# Ergots

| | |
|---|---|
| Indication | •They are only used to abort the attacks [ Exception Dihydroergotamine can be given for severe, recurrent attacks ]<br>•Their use is restricted to patients with frequent, moderate attack or infrequent but severe attacks. " Never give it in Recurrence or Prevention only in abortive therapy" |
| Adverse effects | •Nausea ,vomiting , abdominal pain and diarrhea<br>•Feeling of cold " due to Vasoconstriction "and numbness of limbs, tingling<br>•Pericardial distress, anginal pain due to coronary spasm, and disturbed cardiac rhythm ( tachycardia or bradycardia ), it rebounds hypertension also<br>•Prolong use → rebound headache due to vasodilatation followed by vasoconstriction.<br>•Prolong use and high dose → paraesthesia & gangrene<br>•Hallucination.<br>•Gangrene in peripheral nerves (fingers) and sexual organs (penis and clitoris) |
| Contraindication | •Pregnancy; fetal distress and miscarriage<br>•Peripheral and coronary vascular diseases, hypertension<br>•Liver and kidney diseases<br>•Fever, sepsis<br>•For prophylaxis of migraine.<br>•In concurrent use with triptans( at least 6 hrs from last dose of tryptans or 24 hrs from stopping ergotamine)<br>•In concurrent use with β-blockers because they have the same action (vasoconstriction) it can lead to HTN or Angina B2 produces V.D, B1 cardiac stimulatory so the antagonist is V.C<br>• Sepsis , fever = we need to increase inflammatory cells to kill the pathogen, so if we give him we do the opposite " vasoconstriction !, can lead to death |

# Triptanes

- Selective
- Agonist at 5HT1 receptors
- At presynaptic trigeminal nerve endings→ decrease release of vasodilating peptides and decrease excessive firing of these nerve endings
- At meningeal, dural, cerebral vessels → decrease vasodilation & stretching of the pain endings.
- No α1, α2, β –adrenergic, dopamine or muscarinic receptors.

| | |
|---|---|
| Sumatripatan | •Present in nasal & injectable forms<br>•Oral bioavailability low / Subcutaneous bioavailability is 97%, peaks after 2 min & t1/2 nearly 2 hours fast " good to give it to student & have exam, or driver" effects within minutes+short acting |
| Zolmitriptan | •Present in nasal & injectable form<br>•Oral bioavailability 40%, peaks after 2 hrs & t1/2 nearly 3 hours intermediate |
| Naratriaptan | •Present in addition + oral preparation<br>•Oral bioavailability 70%, peaks after 2 hrs & t1/2 nearly 6 hours slow_+long acting |

# Triptanes

| | |
|---|---|
| Indication | •To abort attacks in patients with frequent, moderate or infrequent but severe attacks<br>•In cluster headache |
| Adverse effects | •Mild pain and burning sensation at the site of injection. From injection<br>•Paraesthesia, tingling ,warmth, heaviness<br>•Flushing / Dizziness<br>•Vasospasm " Not good to HTN & Angina patients"<br>•Ischemic heart; Angina → M.I<br>•Hypertension, Arrythmias<br>•Zolmitripan will cause: Chest & neck tightness and Somnolence |
| Contraindication | •Peripheral vasospastic diseases<br>•Uncontrolled hypertension<br>•History of ischemia<br>•Cerebrovascular disorders<br>•In concurrent use with ergots or others inducing vasospasm } Rizo & Zolmitriptan<br>•In concurrent use with MAO Is, lithium, SSRIs, ….→(5HT) } Rizo & Zolmitriptan<br>• Renal or hepatic impairment } Naratriptan |

# B- prevent recurrence

You have to know the groups and the names of the drugs in each group.
You won't be asked about details!

| | |
|---|---|
| Antispastic muscle relaxants | Botulinum toxins, Tizanidine |
| Antiepileptics | Block Na channel & augment GABA at GABA-A receptors<br>• Topiramate; weight loss & dysthesia<br>•Valproic; weight gain, hair loss, polycystic ovary → not given to young females<br>•Gabapentin |
| Antidepressants | •Pizotifen; Like TCA + 5HT2 antagonist + mild antimuscarinic & anti-histaminic activity. Drowsiness, ↑appetite →weight gain. Not given with other CNS depressants → sedation. Not given with MAO Is<br>•TCA (tri cyclic anti-depressent) Ami & nortriptyline →Dopamine antagonists<br>•SSRIs |
| Antihypertensives<br>" has a role in prophylactic " | •Beta-blockers; Propranolol, atenolol, metoprolol, Not in young & anxious nor in elderly & depressed, diabetic...etc<br>•Ca Channel Blockers<br>•ACEIs lisinopril & ARBs candesartan |

# Deciding Whether Better With A Triptans Or With Dhe.

- For patients with headache episodes lasting 2 or 3 days at a time, DHE is often the optimal choice because of long $t_{1/2}$.
- For patients with migraines a day or less and need rapid relief of pain, Triptans are often a better choice.

- Injectables
  - Sumatriptan 6 mg
- Orally Disintegrating Tablets
  - Zolmitriptan 2.5 mg and 5 mg
  - Rizatriptan 5 mg and 10 mg
- Nasal Sprays
  - Sumatriptan 20 mg
  - Zolmitriptan 5 mg (not currently available in the US)
  - DHE-45
  - Butorphanol nasal spray (for rescue and CV risk factor patients)

**The form of drug preparation could influence the choice**

* Injectable sumatriptan reaches $T_{max}$ the fastest followed by DHE nasal spray and rizatriptan
* DHE nasal spray, naratriptan, eletriptan, and frovatriptan have lower recurrence rates

# CHOOSING A TRIPTANS

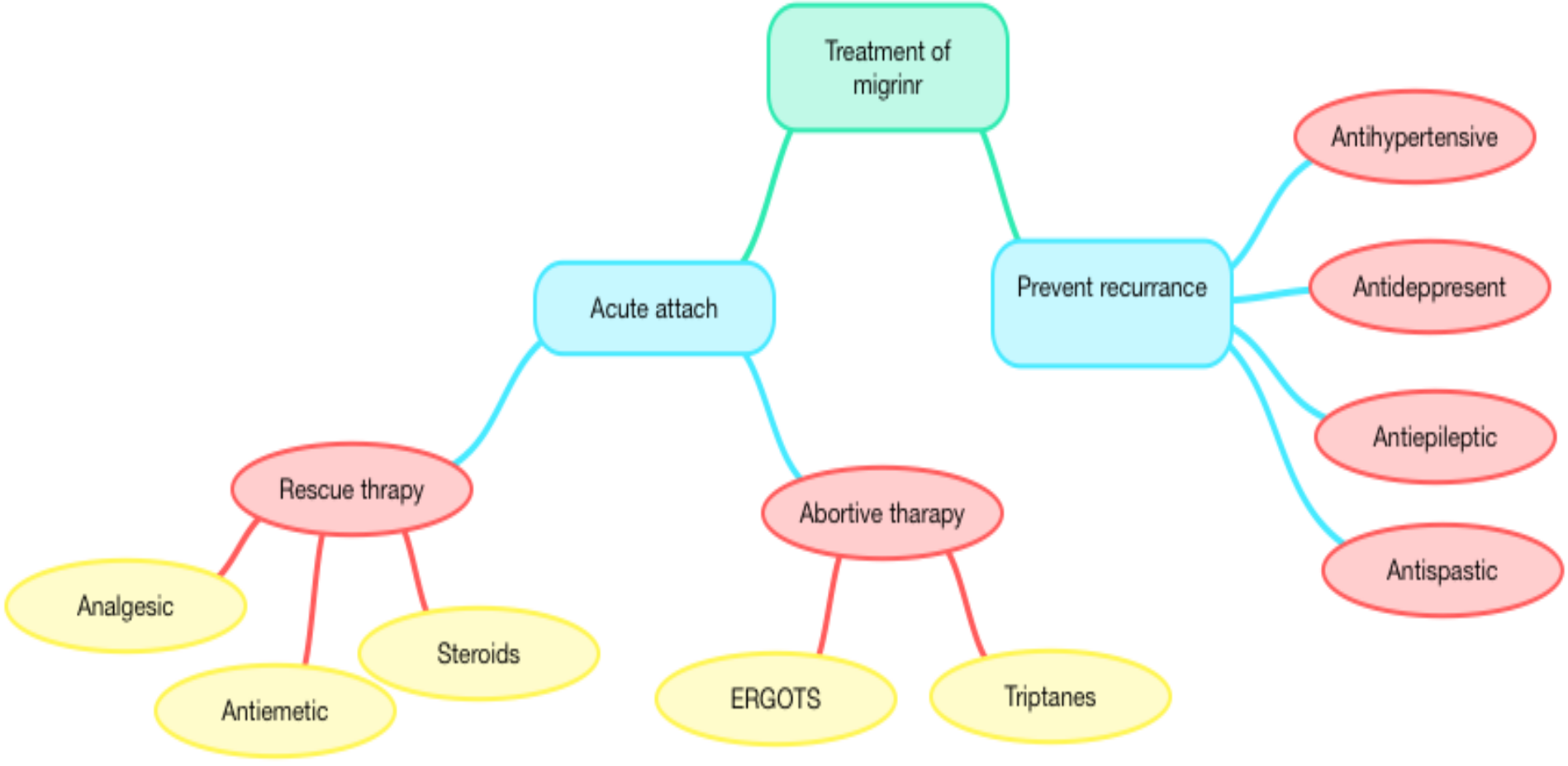
- Differences in the time to peak blood concentration $T_{max}$, equates with faster relief of head pain.
- Differences in $t_{1/2}$ → a clinical effect in terms of recurrence of headache

Pharmacokinetics

| Medication | $T_{max}$(h) | $t_{1/2}$(h) |
|---|---|---|
| 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 |

- For extremely fast relief within 15 min. injectable sumatriptan is the only choice.
- If onset could start within a couple of hrs, oral rizatriptan, zolmitriptan, eletriptan, or sumatriptan nasal spray are appropriate choices
- If expected re-dosing is needed & / or recurrence of headache Naratriptan , frovatriptan, have slower onset, fewer side effects, and a lower recurrence rate

# SUMMARY






Slides Important Doctor's Notes Explanation

# QUESTIONS

**1- which one of the following drugs is contraindicated in case of renal failure ?**

A-Naratriaptan B-Zolmitriaptan C-Valproic D- Dihydroergotamine

**2- 40-year-old woman presents with chronic migraine headaches.**
**She reports that once a month she has a severe, unilateral headache associated with nausea and vomiting. The headache will last for a full day if not treated.**
**She has had success in reducing the severity of the headaches with opioid medications, but usually she is too nauseous to take them. She is missing about a day of work when the headache comes .. Which one of the following drugs is best to treat her next headache?**

A- ergotamine B-sumatriptan C-odansetron D-valporic acid


1-A
2-B

# QUESTIONS

**3- 20-year-old man presented with migraine headaches.**
**He was in medication, now he is suffering from Chest & neck tightness and Somnolence, which one of the following drugs could cause this.**

A- ergotamine B-Zolmitriaptan C-Valproic D- Dihydroergotamine

3-B

# THE END


*Leaders*

*Abullah AL-Anazi & Tuqa Alkaff*

*E-Mail*

*pharmacologyteam1@gmail.com*