DRUGS USED IN HEADACHE & MIGRAINE

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ILOs

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

HEADACHE

Pain anywhere in the region of the head or neck

It is caused by disturbance of the
Pain – Sensitive Structures around the brain

Within the cranium

(blood vessels, meninges, cranial nerves)

Outside the cranium

(muscles, nerves, arteries, veins, subcutaneous tissues, eyes, ears & other tissues).

MIGRAINE

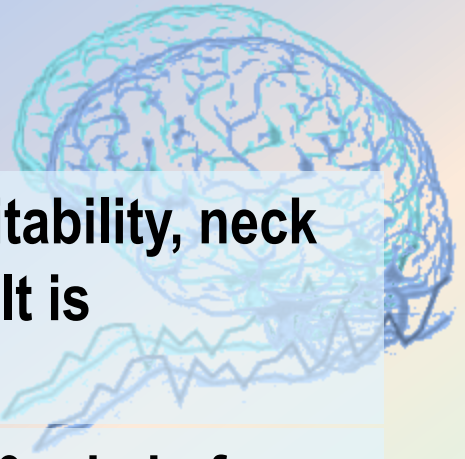
Recurrent attacks of throbbing headache
Unilateral / or on both sides
Lasting from > 2 up to 72 hrs.
+ Preceded *(or accompanied)* by AURA

Perceptual disturbance of motor < sensory nature
visual [Photophobia (↑sensitivity to light)]
auditory [Phonophobia (↑ sensitivity to sound)]
olfactory unpleasant smell ….
Sensory; abnormal sensation at face, extremities.
Develops over 5-20 min & last fewer than 60 min.

Aura: flashes of light, blind spots or tingling in your arm.

Migraine pain is usually on one side of head with facial & neck pain, nausea & vomiting.

Phases of Migraine



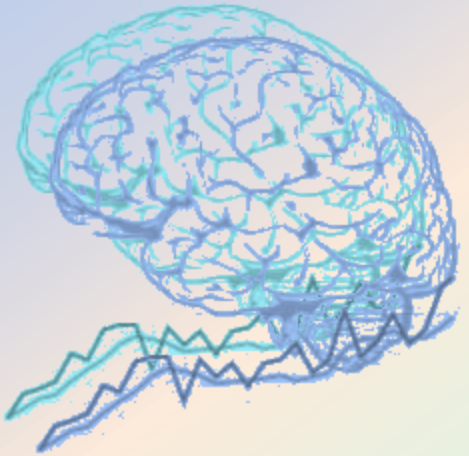
1. Prodrom Phase; a change in mood or behavior (irritability, neck stiffness) that starts hours or days before headache. It is experienced by 60% of migraineurs.

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. Postdrom Phase: still not normal, either;
•More likely fatigued → irritability /impaired concentration /scalp tenderness /mood changes / GIT symptoms, ……

Migraine Triggers



Diet Aged cheese, Alcohol, Chocolate, Caffeine, Hot dogs, Avocado, Fermented or pickled foods, Yeast or protein extracts.

Stresses

Hormonal changes: Menstrual migraine

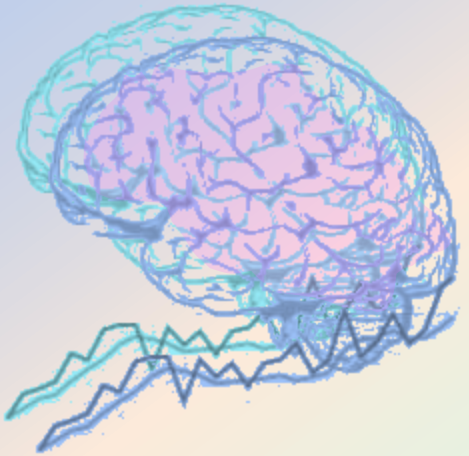
Climate

Diseases

Therapy Antibiotics, Antihypertensives, H_2 blockers, Vasodilators, Oral contraceptives.

Life Style

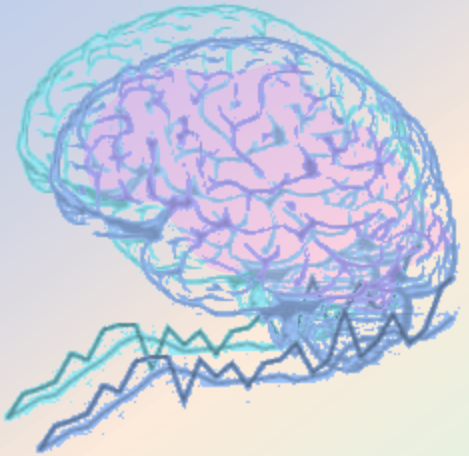
Migraine Causal Theories



- Vascular
- Cortical Spreading Depression
- Neurovascular theory ?
- Mediators [Serotonin]
- Dopaminergic Hypersensitivity

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

Migraine Causal Theories



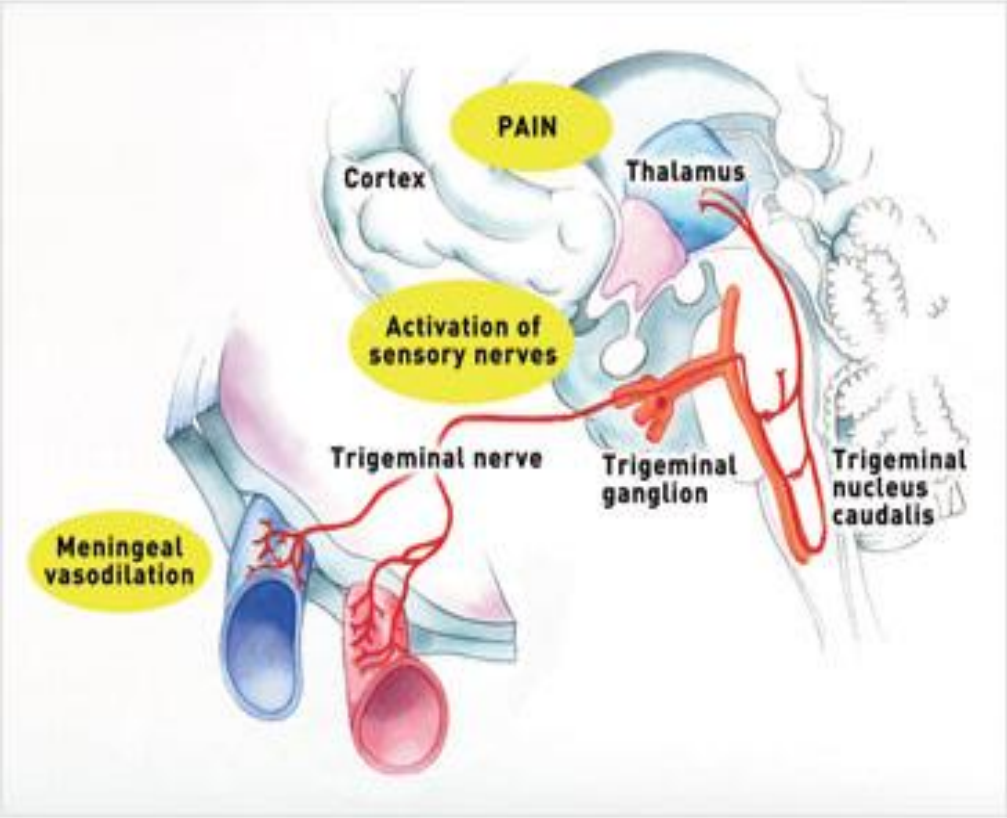
Vascular

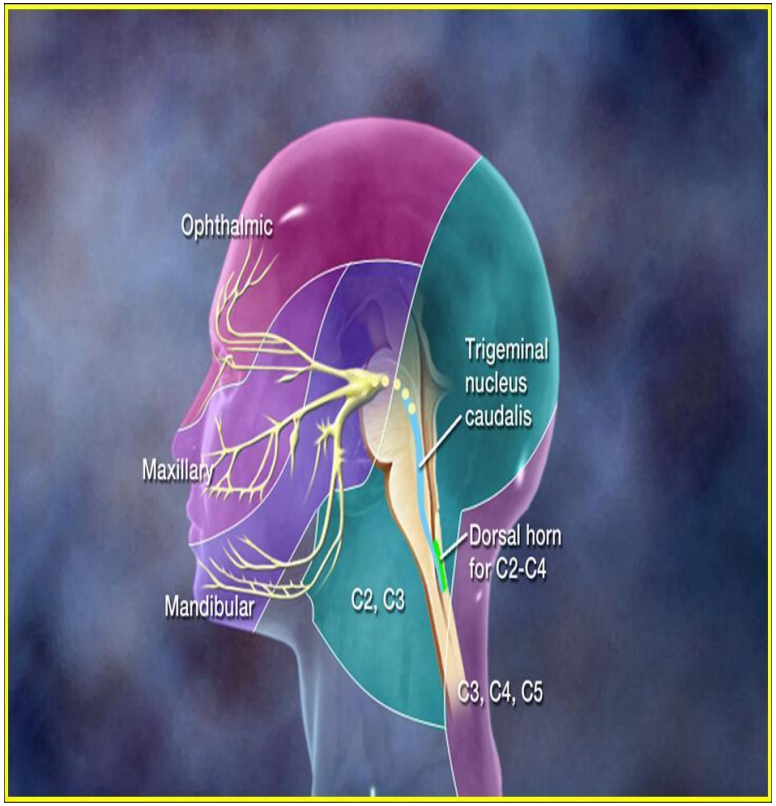
Neurovascular theory ?

Mediators [Serotonin]

Dopaminergic Hypersensitivity

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 trigeminovascular 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 & neck pain, experienced during migraine.

TREATMENT STRATEGY

ACUTE ATTACK

Controls attack.

RESCUE THERAPY

Non-specifically target individual symptoms i.e. alleviating pain, emesis & associated symptoms

Mild-Moderate

ABORTIVE THERAPY

They specifically target pathways of migraine by
⬇ meningeal dilatation &
⬇ neural activation via $5HT_1$ agonism ➔ i.e. stopping headache as it is evolving.

Abortive medications > effective if taken early, just before the pain starts, losing effectiveness once the attack has begun

So they must be rapidly acting

Severe/ Disabling

PREVENT RECURRENCE

⬇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*

TREATMENT of Acute Attack

RESCUE THERAPY

➔ **Analgesics**

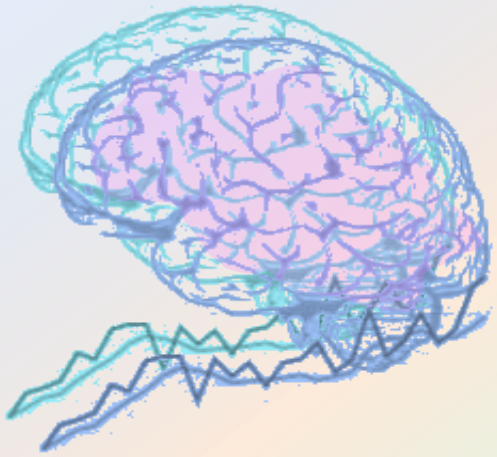
- NSAIDs / Aspirin< Acetaminophen
- (ibuprofen, naproxen for mild to moderate attack with no nausea & vomiting)
- Opioid-like drugs: μ agonist; e.g. Tramadol.

➔ **Antiemetics**

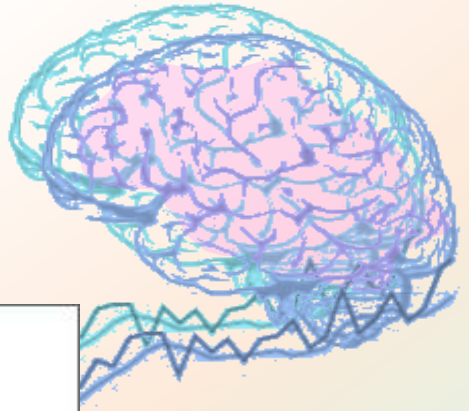
- Dopamine Antagonists + ***Gastro-prokinetic***
  - Domperidone

↑ ***Absorption & bioavailability of abortive therapy***

- ***Phenothiazines*** — ***Dopamine antagonists + Sedation***
  - Promethazine
- $5HT_3$ antagonists (for severe nausea & vomiting)
  - Ondanseteron
  - Granisetron
- H_1 antagonist — ***Antihistamine +sedation Anticholinergic***
  - Meclizine, diphenhydramine



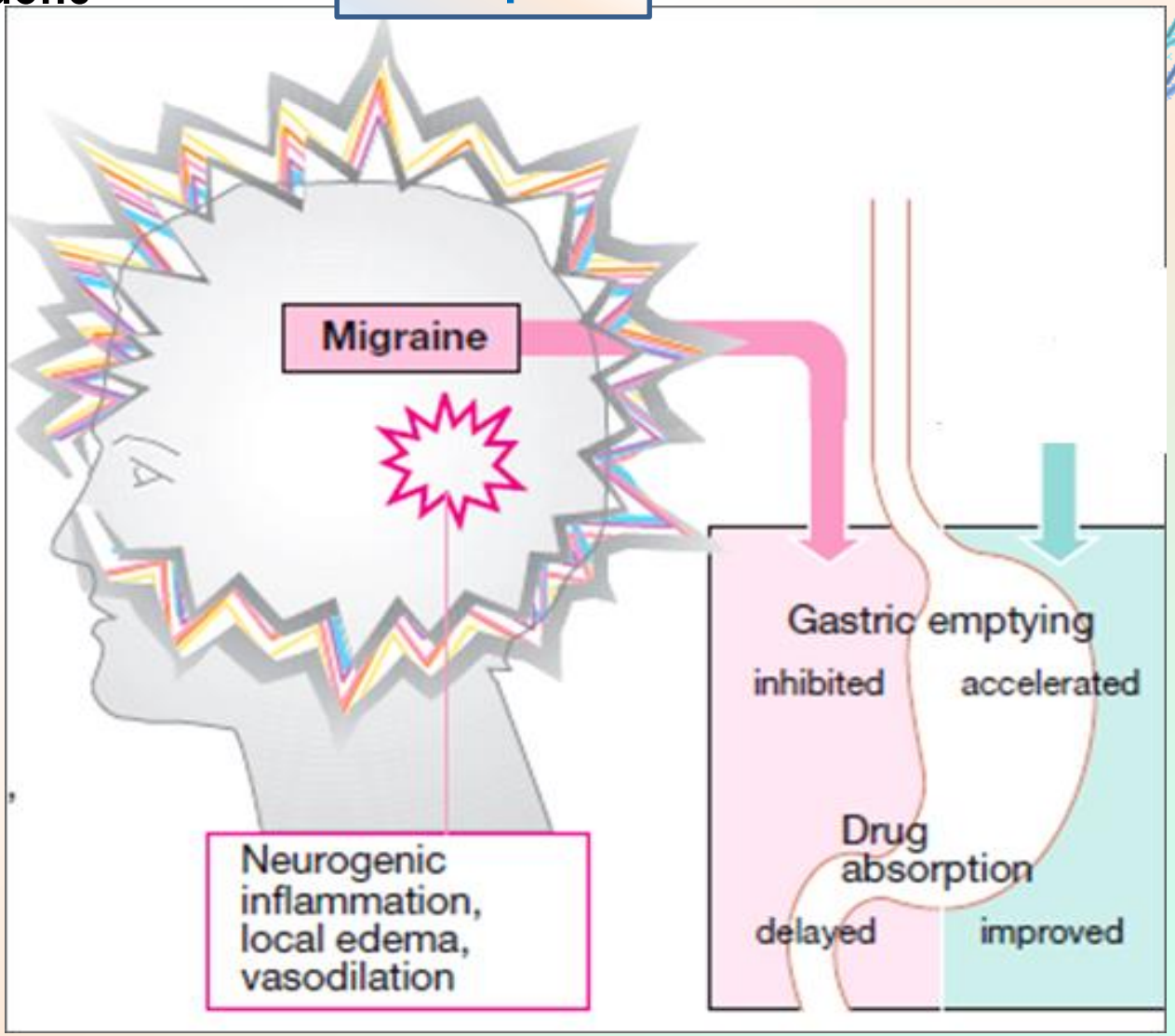
TREATMENT of Acute Attack



Prokinetics;

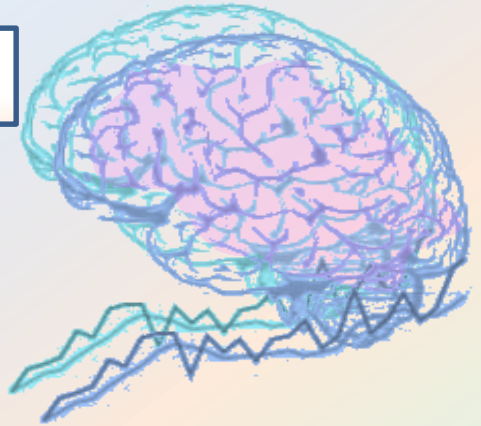
Domperidone

Help Absorption



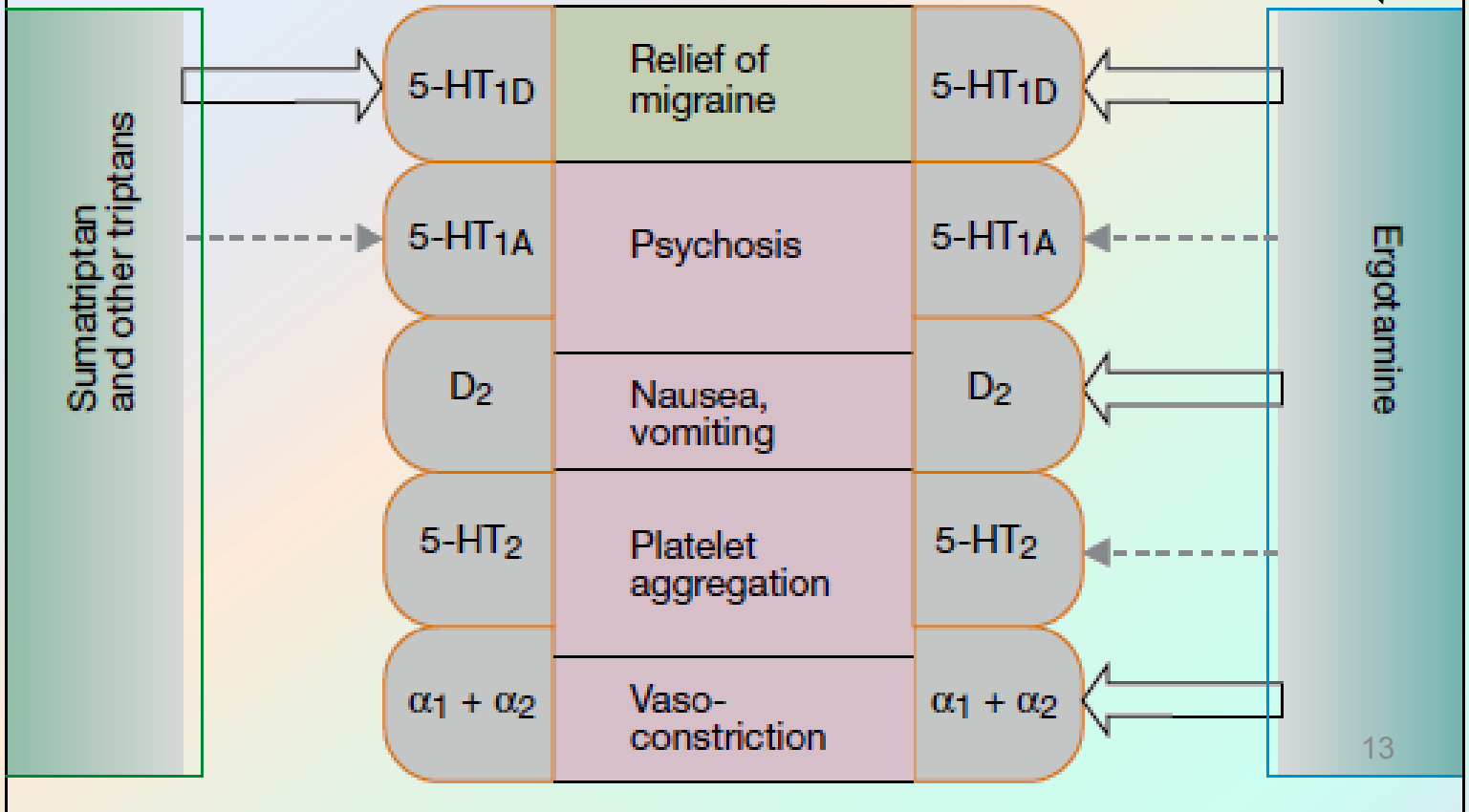
TREATMENT of Acute Attack

ABORTIVE THERAPY



➔ $5HT_1$

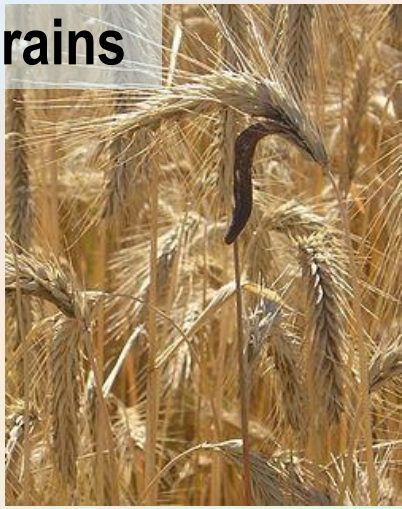
- **AGONISTS** ➔ **TRIPTANS**
  > selective
- **PARTIAL AGONISTS** ➔ **ERGOTS**
  non-selective



TREATMENT of Acute Attack

ABORTIVE THERAPY

ERGOTS



Product of *Claviceps purpurea;* a fungus growing on rye/ grains

Non-Selective

Partial agonism at $5HT_1$ receptors (5HT-1D/1B found in cereberal & menigeal 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

Ergotamine tartarate (resticted use)

Oral, sublingual, rectal suppository, inhaler

↑

Caffeine → Cafergot

Dihydroergotamine (DHE)

Nasal spray, inhaler & injectable forms (good to use if patient is vomiting)

Ergotamine tartarate (rare clinical use due to severe adverse effects

Oral absorption **Incomplete (erratic) + slow → low bioavailability**

Despite $t_{1/2}$ nearly 2 hours, ergotamine produces vasoconstriction → 24 hours or longer due to high & long tissue binding ability.

Ergotamine tartrate has significant side effects, & may worsen the nausea & vomiting associated with migraine.

DHE (preferred in clinical setting)

Given parenterally, DHE is eliminated more rapidly than ergotamine, presumably due to its rapid hepatic clearance & has less adverse effects.

Indications

They are only used to abort the attacks [*Exception DHE 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 & numbness of limbs, tingling
- Anginal pain due to coronary spasm, & disturbed cardiac rhythm (tachycardia or bradycardia)
- Prolong use → rebound headache due to vasodilatation followed by vasoconstriction.
- Prolong use & high dose → paraesthesia (tingling or burning sensation).

Contraindications

- Pregnancy; fetal distress & miscarriage (ergot is uterine stimulant & vasoconstrictor)
- Peripheral & coronary vascular diseases
- Hypertension
- Liver & kidney diseases
- prophylaxis of migraine
- In concurrent use with triptans (at least 6 hrs from last dose of triptans or 24 hrs from stopping ergotamine & β-blockers.

Selective

Agonism at $5HT_1$ receptors

Same as discussed for ergotamine except that triptans are more selective as serotonergic agonist.

No α_1, α_2, β –adrenergic , dopamine or muscarinic receptors.

Triptans inhibit the release of vasoactive peptides, promote vasoconstriction, & block pain pathways in the brainstem.
Triptans inhibit transmission in the trigeminal nucleus caudalis.

SUMATRIPTAN *Present in →oral, nasal spray, & injectable forms*

Oral bioavailability low / Subcutaneous (SC) bioavailability is 97%, peaks after 2 min & $t_{1/2}$ nearly 2 hours (fast action with Sc, good for patient with vomiting)

ZOLMITRIPTAN *Present in →nasal spray, & injectable forms*

Oral bioavailability 40%, peaks after 2 hrs & $t_{1/2}$ nearly 3 hours

NARATRIPTAN *Present in addition → + Oral preparations*

Oral bioavailability 70%, peaks after 2 hrs & $t_{1/2}$ nearly 6 hours (slower onset, less side effects).

TRIPTANS

Indications

- To abort attacks in patients with frequent, moderate or infrequent but severe attacks.
- In cluster headache

ADRs

- most of ADRs are the 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.

Contraindications

- 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.

- For patients with headache episodes lasting 2 or 3 days at a time, DHE is often the optimal choice because it has longer $t_{1/2}$
- For patients with migraines a day or less & need rapid relief of pain, Triptans are often a better choice
- For pregnant women: paracetamol or intranasal sumitriptan & or diphenhydramine, meclizine are safe to be used.

The form of drug preparation could influence the choice

Injectable sumatriptan reaches T_{max} the fastest followed by DHE nasal spray & rizatriptan.

CHOOSING A TRIPTAN

- 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

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

CHOOSING A TRIPTAN

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, & a lower recurrence rate**
- Menstrual migraine: Frovatriptan (longer half life (26 hrs) 2.5 mg twice per day beginning 2 days before the anticipated onset of menstrual migraine & continuing for 6 days.

TREATMENT STRATEGY

ACUTE ATTACK

Antiepileptics;

Block Na channel & augment GABA at GABA-A receptors

e.g. Topiramate;

Valproic;

PREVENT RECURRENCE

Antidepressants

TCA; amitriptyline & nortryptyline

Antihypertensives

β-blockers

e.g. propranolol

Propranolol is commonly used in prophylaxis of migraine attack.