Pharmacology Team 431

(CNS BLOCK)

Drugs used in headache and migrane

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At the beginning you have to know:

1- there are types of headache and we differentiate between them according to their symptoms ,signs and pathophysiology.

2-headache is caused due to disturbance in pain(sensitive) structures around the brain.

3- Its important to know the pathophysiology of headache and migraines thus you can decide how to deal with it , either by preventing it (**using preventive therapy**) or by treating it **(using abortive therapy**).

So mechanism of drug will differ according to the aim of using it:

-Preventive therapy: It will inhibit the vasoconstriction (to not lead to vasodilation) so all the drugs are **vasodilators** (eg; antihypertensive drugs).

- Abortive therapy : It will inhibit the vasodilation (because the patient is already has the headachethe vessel is dilated) so all the drugs are **vasoconstrictors** (eg: ergots).

#Headache: Pain anywhere in the region of the head or neck.

It is caused by disturbance of the

Pain – Sensitive Structures around the brain.

"we haven't added the theories ,the phases and triggers of the migraine, you can read it from the slides"

Classifications and general treatment of headaches:

-Primary : **Migraine, tension type headache, cluster headache, trigeminal cephalgias and others where cause in unknown => in most we use NSAIDs.**

-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, hypothroidsm. => TREAT the etiology.

MIGRAINE

Aura : is perceptual motor < sensory disturbance in visual (photophobia) or auditory(phonophobia) and olfactory unpleasant smell. Preceded the attack 5-20 minutes, and when patient develops aura he knows that he will develop migraine .

Recurrent attacks of throbbing headache.

Unilateral / or on both sides

Lasting from > 2 up to 72 hrs.

+ Preceded *(or accompanied)* by AURA

there are 2 types of migraine

_classic : with aura (20%)

_commen : without aura (80%).

TREATMENT OF MIGRAINE

-Acute attack:

Controls attack.

- non-specific : RESCUE THERAPY -> Non-specifically target individual symptoms i.e. alleviating pain, emesis and associated symptoms (routine drugs e.g. : NSAIDs)

- specific : ABORTIVE THERAPY -> They specifically target pathways of migraine by ê meningeal dilatation & ê neural activation via 5HT1 agonism è i.e. stopping headache as it is evolving.

*** Abortive medications** > effective if taken early before the dilation of vessels, losing effectiveness once the attack has begun >> **So they must be rapidly acting**

Mild-Moderate => **Give rescue therapy**
Severe/ Disabling => **Give abortive therapy**

-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 months& can be repeated.

-Rescue therapy:

➔ Analgesics

1- **NSAIDs** / Aspirin< Acetaminophen

2-Non-opioid: **m** agonist; **Tramadol** (mild narcotic analgesic) - *act on 5HT & NE*

➔ Antiemetics

A-Dopamine Antagonists : **Domperidone** (has anti emetic effect dopamine antagonist drug).

***it has Gastro-prokinetic effect** **(it empties the stomach so reduce the sense of nausea and vomiting)**

***it enhances the absorption and bioavailability of abortive therapy.**

B-Phenothiazines: **Promethazine**

***It has dopamine antagonistic effect.**

***Sedation.**

Because we don't like sedative effects in treatment of migraine with sedative drugs so we chose the least sedative effect from phenothiazine's group which is "promethazine" .

C- $5HT_3$ antagonists: **Ondanseteron -Granisetron**

D– H_1 antagonist: **Meclizine (antihistaminic and anticholinergic)**

Others .. Steroids

5 HT3 antagonists is most potent antiemetic and its used only in vomiting accompained postoperative conditions and in cancerous patients.

In Migraine we only use it in severe cases of vomiting accompanied It.

-Abortive therapy:

*5HT1:

1-Selective: agonist → TRIPTANS
2-Non-selective: partial agonist → ERGOTS

ERGOTS acts also on 5HT2, dopamine, alpha adrenergic receptors.

Once ergots has alpha sympathetic activity it has vasoconstricting effect.

Rescue therapy: help the absorption of abortive therapy
Gastroprokinetics; Domperidone

Prokinetic effect of Domperidone enhances the abortive therapy if its orally administrated we combined it with it .

Our goal in abortive therapy is to decrease the cerebral vasodilatation in the pain sensitive areas of brain. And these drugs act on 5HT 1 receptors as agonists.

1-ERGOTS

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

***Non-Selective, Agonism of $5HT_1$ receptors**

At presynaptic trigeminal nerve endings (which supply meningeal blood vessel):
↓release of vasodilating peptides
↓excessive firing of these nerve endings

agonism effect on 5HT1 receptors will be on nerve endings by decrease the firing rate and in blood vessles decrease vasodilation and decrease the exudates that induce migraine

At blood vessels :

↓vasodilation & stretching of the pain endings
↓ transmitter release in the perivascular space.

***Partial agonist effect on α-adrenoceptors → vasoconstriction**

Antagonist to some dopaminergic & serotonergic receptors

This is only characteristic to ergots.

· **Ergotamine tartarate:** Oral (very slow), sublingual, rectal suppository (better), inhaler & injectable forms.
The oral preparation is slow so once we add caffeine the absorption will increase .

· **Dihydroergotamine :** Nasal spray, inhaler & injectable forms

Ergotamine tartarate

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

Dihydroergotamine

Dihydroergotamine is eliminated more rapidly than ergotamine, presumably due to its rapid hepatic clearance.

Indications of ergots:

They are only used to abort the attacks [*Exception Dihydroergotamine can be given for severe, recurrent attacks*]

Their use is restricted to patients with frequent, moderate attack or infrequent but severe attacks.

ADR:

- **GIT upset**
- **Feeling of cold and numbness of limbs, tingling**
- **Pericardial distress, anginal pain due to coronary spasm, and disturbed cardiac rhythm (tachycardia or bradycardia)**
- **Prolong use → rebound headache due to vasodilatation followed by vasoconstriction.**
- **Prolong use and high dose → paraesthesia & gangrene**

Contraindications

- **Pregnancy; fetal distress and miscarriage**
- **Peripheral and coronary vascular diseases**
- **Hypertension**

Never take ergots as a prophylaxis because of its vasoconstricting effect.only abortive!

- **Liver and kidney diseases**
- **For prophylaxis of migraine.**
- **In concurrent use with triptans(at least 6 hrs from last dose of tryptans or 24 hrs from stopping ergotamine)**
- **In concurrent use with β-blockers**

Because of blocking action on B2 receptor in blood vessels causing vasoconstriction thus we cannot give Beta blockers with ergots as it has the same action " vasoconstriction".

2-TRIPTANES (ABORTIVE THERAPY-TREATMENT of Acute Attack)

Selective

Agonism at $5HT_1$ receptors like ergot

But with no α_1, α_2, β – adrenergic , dopamine or muscarinic receptors. " so less side effects"

***SUMATRIPTAN : Present in →nasal spray, and injectable forms**

Oral bioavailability low / Subcutaneous bioavailability is 97%, peaks after 2 min & $t_{1/2}$ nearly 2 hours .

***ZOLMITRIPTAN: Present in →nasal spray, and 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

Indications of triptanes:

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

Most of the adverse effects because of vasoconstriction

ADR :

1-Mild pain and burning sensation at the site of injection.

2-Paraesthesia, tingling ,warmth, heaviness

3-Flushing / Dizziness

4- Vasospasm

5-Ischemic heart; Angina → M.I

6- Hypertension

7- Arrhythmias

ZOLMITRIPTAN ADR :

1-chest & neck tightness.

2-somnolence.

Contraindications:

1. Peripheral vasospastic diseases.
2. Uncontrolled hypertension.
3. History of ischemia.
4. Cerebrovascular disorders.
5. In concurrent use with ergots or others inducing vasospasm.
6. In concurrent use with MAO Is, lithium, SSRIs, ….→(5HT)=not given with antidepressant drugs (it react with them)
7. Renal or hepatic impairment (specially with *NARA > RIZOTRIPTAN*)

Note that first 6 points of contraindications are contraindicated especially with RIZO&ZOLMITRIPTAN

NB: TRIPTANs are better than ERGOTs for patients who have cardiac diseases because they have minimal constriction effect

Deciding whether to use TRIPTANs or ERGOTs:

–For patients with headache episodes lasting 2 or 3 day DHE is often the optimal choice because it has longer t1/2

- For patients with migraines a day or less and need rapid relief of pain, Triptans are often a better choice(Because it's rapid in onset and short duration)

-Subcutaneous Injectable Sumatriptan reaches Tmax the fastest followed by DHE nasal spray and Rizatriptan (the suitable choice of rapid relive of pain is injection _eg: sumatriptan_ then nasal spray and the lowest onset is oral preparation so we can choose the preparation according to how urgent is the case)

- DHE nasal spray, Naratriptan, Eletriptan, and Frovatriptan have lower recurrence rates .(we can use these drugs in treatment of patient with more than 3 attacks in month)

CHOOSING A TRIPTAN:

- Differences in the time to peak blood concentration T_{max}, equates with faster relief of pain.(to have rapid relive of pain we choose drug that have rapid onset)

-Differences in t1/2 → a clinical effect in terms of recurrence of headache(to prevent the recurrence ,we choose the longest drug duration)

Important points:

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

2- If onset could start within a couple of hours, oral Rizatriptan, Zolmitriptan, Eletriptan, or Sumatriptan nasal spray are appropriate choices

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

Drug that PREVENT RECURRENCE:

1-Antispastic muscle relaxants(it inhibit the contraction):
Botulinum toxins, Tizanidine
2-Antihypertensives:
-Ca Channel Blockers
-beta-blockers

3-Antidepressants

4-Antiepileptics

Questions:

- Which one of the following drugs can cause gangrene, Ischemia and it's used only in acute attacks :

1- sumatriptan
2- dihydroergotamine
3- aspirin
4- odansetron

- 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 :

1- ergotamine
2- sumatriptan
3- odansetron
4- valporic acid

Answer: 2 , 2