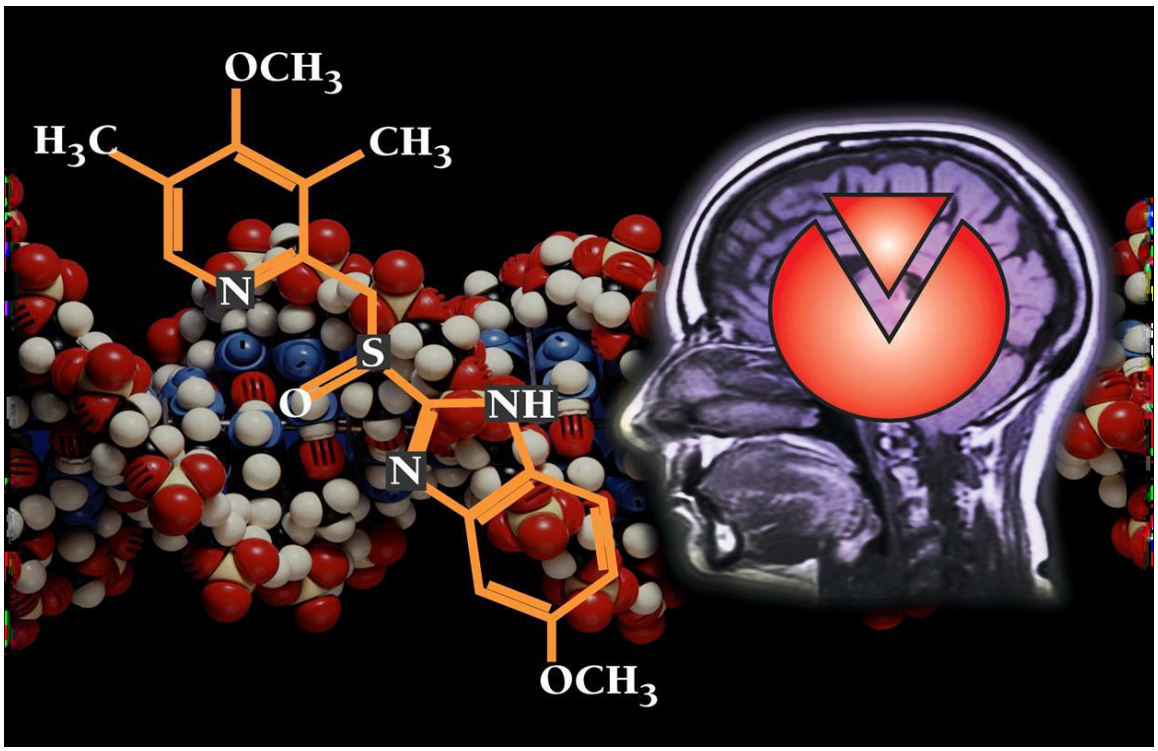
King Saud University
College Of Medicine
Pharmacology Team 430
CNS Block

Drugs used in headache and migraine



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First of all..

You should know the pathophysiology of headaches and migraines to decide how to deal with it, either by preventing it (using preventive therapy) or by treating it (using abortive therapy)

The pathophysiology of headaches :

It occurs by **prolonged vasoconstriction** which ends in **vasodilation** (as protective mechanism from the body), this vasodilation irritates the meninges that surrounds it and stimulates its nociceptors, then **we feel the headache** (so the **main cause is rebound vasodilation**)

Therefore the mechanism of the 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 headache_ the vessel is dilated__) so all the drugs are vasoconstrictors (eg; ERGOTs)

Classification & General Treatment of Headaches :

- Primary:

Migraine, tension type headache, cluster headache, trigeminal cephalgias and others where cause is unknown → **in most we use: NSAIDs**

- Secondary:

Based on the etiology

- **Trauma:** of head or neck
- **Vascular disorders:** ischemic stroke, intracranial hemorrhage.
- **Disease:** intracranial tumors, infection,
- **Homeostasis disorders:** high BP, fastening, hypothyroidism.
- Others……

→ **we treat the etiology**

MIGRAINE:

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

AURA : Many times, migraine headaches are preceded by some sort of symptoms like ..visual disturbance and emesis ..etc known as an Aura. They usually occur minutes to hours before the pain of a migraine starts. Sometimes it may be accompanied with the migraine or continue for awhile after the migraine.

Rx: Migrains

Rx = Treatment

*** Prevent recurrence:**

- ↓recurrence frequency, severity, duration & / or disability
- ↑responsiveness to abortive therapy

Mild-Moderate → Give **rescue** therapy

Severe/ Disabling → Give **abortive + rescue** therapy

N.B **if the patient usually suffers from the recurrence attack he should take preventive therapy to reduce the recurrences.** Full effect of therapy needs several weeks to manifest & should continue for 6 months & can be repeated.

***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 ↓ meningeal dilatation & ↓ neural activation via $5HT_1$ agonism → 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

I) RESCUE THERAPY:

1] Analgesics:

- NSAIDs / Aspirin< Acetaminophen
- Non-opioid: μ agonist; Tramadol - *act on 5HT & NE receptors*
- Sedatives; Butalbital

2] Antiemetics:

A) Dopamine Antagonists : Domperidone (less sedative + has anti emetic effect dopamine antagonist drug)

- + Gastro-prokinetic (it empties the stomach so reduce the sense of nausea and vomiting)
- ↑ Absorption & bioavailability of abortive therapy

B) Phenothiazines :

Promethazine

- Dopamine antagonists
- Sedation(we don't like too much sedative effect in treatment of migraine so we choose the least sedative effect from phenothiazine's group which is Promethazine)

C) $5HT_3$ antagonists : Ondanseteron - Granisetron

D) H_1 antagonist : Meclizine (*Antihistamine* + *Anticholinergic*)

Others; Steroids

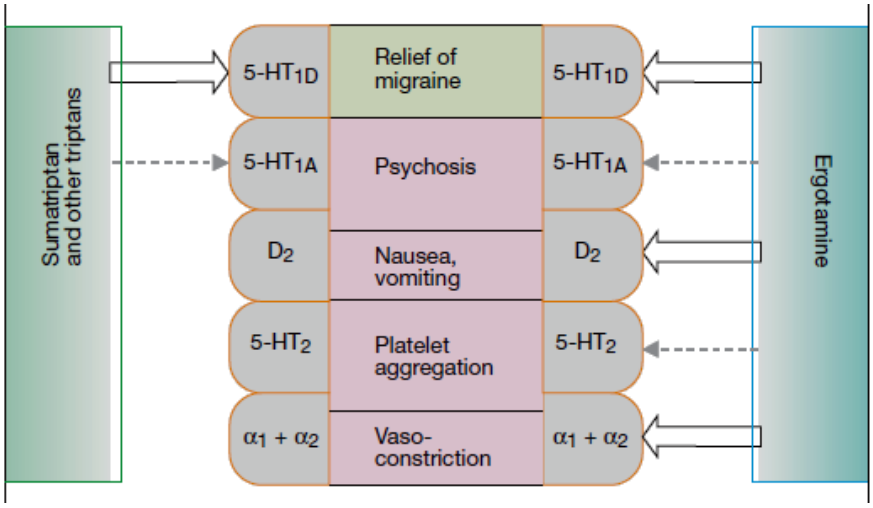
II) ABORTIVE THERAPY:

- **$5HT_1$:**

Selective: agonist → TRIPTANS

Non-selective: partial agonist → ERGOTS

- **CGRP(Calcitonin gene-related peptide) :** antagonist



Rescue therapy: help the absorption of abortive therapy

Gastroprokinetics; Domperidone

A)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

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

It divides into two types according to the preparation and the durations:

- **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 this combination is called **Cafergot**

- **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 t1/2 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:

1. They are only used to abort the attacks [Exception Dihydroergotamine can be given for severe, recurrent attacks]
2. Their use is restricted to patients with:
   - frequent, moderate attack
   - infrequent but severe attacks

ADRs of ERGOTS:

- **Nausea ,vomiting** , abdominal pain and diarrhea
- Feeling of cold and **numbness of limbs, tingling**(because of the vasoconstriction)
- **Pericardial distress, angina** due to coronary spasm, and disturbed cardiac rhythm (tachycardia or bradycardia)
- **Prolonged use** → rebound headache due to vasodilatation followed by vasoconstriction.(the drug is a vasoconstrictor and when we use it for a long time the body does vasodilation for protection → dilation of blood vessels will stimulate the nociereceptors and we'll feel a headache again)
- **Prolonged use and high dose** → Paraesthesia & gangrene(because of the vasoconstriction)
- **Hallucination**(due to disturbance of blood flow)

  N.B:
  Gangrene is death of cells (necrosis) due to reduce of blood supply

Contraindications:

- Pregnancy; fetal distress and miscarriage
- Peripheral and coronary vascular diseases
- Hypertension
- Liver and kidney diseases
- Fever, sepsis(because in this case we need vasodilation not vasoconstriction)
- For prophylaxis of migraine.
- In concurrent use with triptans(at least 6 hrs from last dose of triptans or 24 hrs from stopping ergotamine)=(because all of them are vasoconstrictors)
- In concurrent use with β-blockers(again because the action of vasoconstriction)

TRIPTANES (ABORTIVE THERAPY-TREATMENT of Acute Attack):

-Selective
-Agonism at 5HT1 receptors
-At presynaptic trigeminal nerve endings→
↓release of vasodilating peptides
↓excessive firing of these nerve endings
-At meningeal, dural, cerebral vessels → ↓vasodilation & stretching of the pain endings .
No α1, α2, β –adrenergic, dopamine or muscarinic receptors(less side effects)

Derivatives of TRIPTAN:

i) SUMATRIPTAN

Present in →nasal spray, and subcutanous injectable (fastest Acting) forms
Oral bioavailability low / Subcutaneous bioavailability is 97%, peaks after 2 min & $t_{1/2}$ nearly 2 hours

N.B:
If the doctor decided to choose TRIPTAN s, this derivative is suitable for patients who used to get headache (sudden in onset (acute) and sustained for short time)

ii) ZOLMITRIPTAN

Present in →nasal spray, and injectable forms
Oral bioavailability 40%, peaks after 2 hrs & $t_{1/2}$ nearly 3 hours

iii) NARATRIPTAN

Present in addition → + Oral preparations
Oral bioavailability 70%, peaks after 2 hrs & $t_{1/2}$ nearly 6 hours (longer duration)

Indications:

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

ADRs:

(Most of them because the effect of vasoconstriction)

Zolmitriptan:

- Chest and neck tightness.
- Somnolence

- Mild pain and burning sensation at the site of injection.
- Paraesthesia, tingling ,warmth, heaviness
- Flushing / Dizziness
- Vasospasm
- Ischemic heart; Angina → M.I
- Hypertension
- Arrhythmias

Contraindication:

The first 6 points are contraindicated specially with

RIZO & ZOLMITRIPTAN

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)*

N.B:
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 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 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 T_{max} 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:

- 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

Drug that PREVENT RECURRENCE:

- Antispastic muscle relaxants(it inhibit the contraction):
  Botulinum toxins, Tizanidine
- Antihypertensives:
  -Ca Channel Blockers
  -b-blockers
  -ACEIs & ARBs
- Antidepressants
- Antiepileptics

Note;

Detailed information about drugs that prevent recurrence are found in the tabels

Summary:

- 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 headache_ the vessel is dilated__) so all the drugs are vasoconstrictors (eg; ERGOTs)
- Drugs that prevent recurrence in migraine are ,Antispastic muscle relaxants(it inhibit the contraction):Botulinum toxins, Tizanidine ,Antihypertensives:,Ca Channel Blockers,b-blockers,ACEIs & ARBs,Antidepressants,Antiepileptics(Toprimate,Valporic acid)
- In an acute attack we have rescue therapy which is non-specific and Abortive therapy which is specific.

I) RESCUE THERAPY:

1] Analgesics: NSAIDs / Aspirin< Acetaminophen,Non-opioid: μ agonist; Tramadol - *act on 5HT & NE receptors*,Sedatives; Butalbital

2] Antiemetics:

A) Dopamine Antagonists : Domperidone ,**Promethazine**, **$5HT_3$ antagonists :** Ondanseteron - Granisetron **,H_1 antagonist** : Meclizine

Others; Steroids

- Domperidone is gastroprokinetic (Improve absorbtion of drugs in Abortive therapy)

II) ABORTIVE THERAPY:

- **$5HT_1$:**Selective: agonist → TRIPTANS**,** Non-selective: partial agonist → ERGOTS

- **CGRP(Calcitonin gene-related peptide) :** antagonist

- Caffeine is used to increase the absorption of ergots
- For extremely fast relief within 15 min. injectable **Sumatriptan** is the only choice.
- For patients with headache episodes lasting 2 or 3 days at a time, DHE is often the optimal choice because it has longer $t_{1/2}$
- Dihydroergotamine is eliminated more rapidly than ergotamine, presumably due to its rapid hepatic clearance