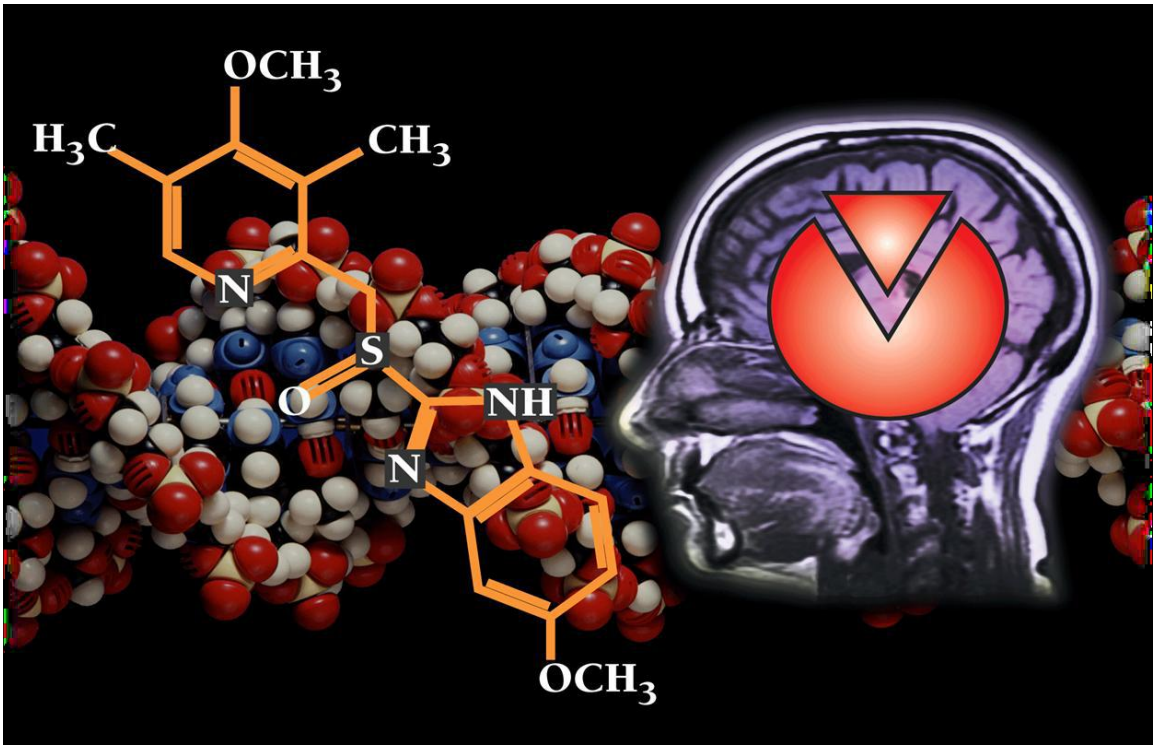
King Saud University
College Of Medicine
Pharmacology Team 430
CNS Block

Drugs related to Balance



Done By:

Mohammed Aldohan

Anfal Alshaya

Aisha Almhbob

Hissah Alballaa

Arwa Abudawood

you should know that all antivertigo drug should have these characters:

1-It works centrally

2-It cross BBB

Drugs used to control or prevent vertigo episodes:

Eg: **it can be used in motion sickness (car sick)**

THERAPEUTIC MANAGEMENT:

1.Prevent Recurrence :

Intend to suppress acute attacks [tame vertigo episodes]:

a) Diuretics (↓ fluid retention) (not loop diuretics eg**: furosemide** because itself induce the vertigo)

Note:
Sometime the congestion of fluid in the inner ear causes electrolyte imbalance then vertigo , so diuretics will be effective as a preventive thereby

b) Corticosteroids (↓inflammation)
Any changes in normal environment can induce inflammation so in vertigo maybe there's inflammatory processes so corticosteroid would be helpful as preventive thereby

c) L-type Ca Channel Blockers (↑ vasodilatation)

d) cinnarazine, flunnarazine, **verapamil**

Note: (these are more specific to the vasculatures of the brain-more selective **to CNS**)_ never use **dihydropyridine** because it's not selective_>
Theses group of drugs cause vasodilatation in middle ear so it'll reduce fluid retention in inner ear

***NB**. Migraine is associated usually with vertigo so if migraine is present → add on its treatment together with the antivertigo drug.*

2. VESTIBULAR SUPRESSANTS:

Intend to dull brain response to vestibular signals from inner ear (so it will reduce the vertigo symptoms which are spinning, vomiting and nausea)

Additional note: Vestibular system:

- There are at least four major neurotransmitters of the vestibular system involved in the *"three neuron arc"*

- Between the vestibular hair cells and oculomotor nuclei that drives the vestibulocular reflex.

- There are also a host of other neurotransmitters which modulate function.

These Neurotransmitter are*:*

Glutamate is the major excitatory neurotransmitter.

Acetylcholine (ACH) is both a peripheral and central agonist affecting muscarinic receptors. Receptors found in the pons and medulla, presumably those involved with dizziness, are almost exclusively of the M2 subtype.

Gamma-aminobutyric acid (GABA) and glycine are inhibitory neurotransmitters found in connections between second order vestibular neurons and onto oculomotor neurons.

Histamine is found diffusely in central vestibular structures and centrally acting antihistamines modulate symptoms of motion sickness.

Norepinephrine is involved centrally in modulating the intensity of reactions to vestibular stimulation and also affects adaptation.

Dopamine affects vestibular compensation, and **serotonin** is involved with nausea

Drugs that ↓Spinning

1) ***H1 agonists + H3 antagonists*** : **Betahistine** **(the first choice)**
2) ***Benzodiazepines :*** promote & facilitate central vestibular compensation via GABA modulation
   e.g.: Lorazepam - Clonazepam - Diazepam
   It's used only if the H1 + H3 antagonist is fail

1) Betahistine *(the best medication for spinning):*

MOA

Betahistine *(selectively decrease spinning):*

1) it has a weak **direct agonistic effect on H1 receptors** located on blood vessels Weak agonist at H1 receptors → regulates inner ear fluid homeostasis (labyrinthine circulation) → inducing vasodilatation in middle ear but not inner ear →(decrease the amount of endolymph) relieves pressure in inner ear

2) Strong **antagonism of H3 autoreceptors** **(are inhibitory presynaptic receptors that inhibit transmitter release)** → **leads to more histamine release to augment effects on H1 receptors in the brain** → ↑ H synthesis in tuberomammillary nuclei of the posterior hypothalamus to promote & facilitate central vestibular compensation↑ H release in vestibular nuclei

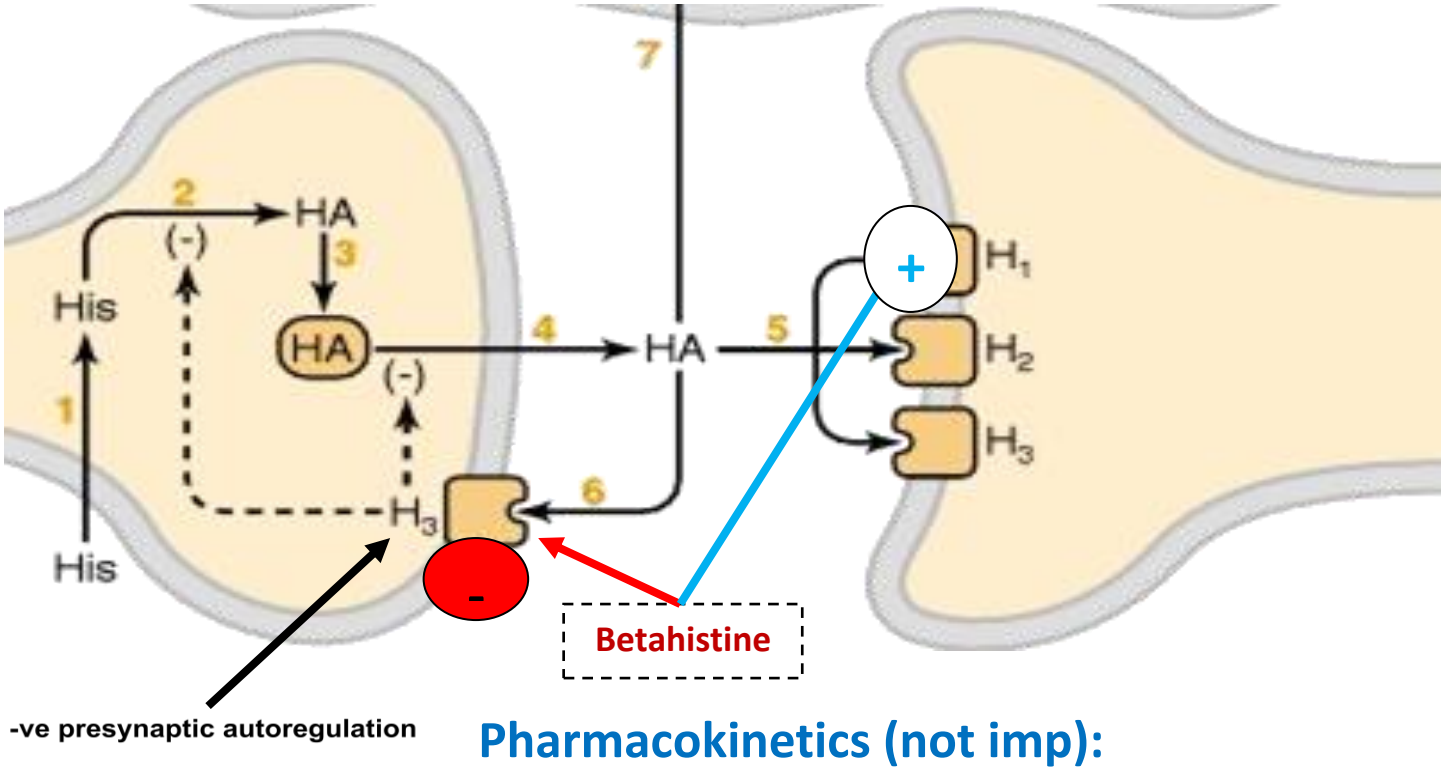
3) it also ↑levels of neurotransmitters such as 5HT in the brainstem, which inhibits the activity of vestibular nuclei.

BETAHISTAMINE can act as vestibular suppressant by 3 ways:

1- increase histamine release (antagonist on presynaptic H3 R) and (act as agonist on post synaptic receptor H1 R) to lower firing in different neuronal areas controlling balance

2- act as agonist in H1 R (vasodilator mainly in middle ear and that will reduce the fluid in inner ear)

3- has effect on serotonin receptor which has a role in inhibiting vestibular neural activity



Pharmacokinetics (not imp):

1. Tablet form , rapidly & completely absorbed
2. t½=2-3h
3. Partially metabolized (active) & excreted in urine

ADRs:

1. Headache
2. Nausea
3. Gastric effects
4. ↓ appetite and weight loss

Contraindication:

1. **Peptic ulcer** *(because it has a gastric affect)*
2. **Pheocromocytoma** *(benign tumor of the adrenal medulla ,it's contraindicated because histamine plays a role in progression of this disease)*
3. **Bronchial asthma** *(because it is a H1 agonist which is bronchoconstriction)*

2- Benzodiazepines

-Lorazepam
-Clonazepam
-Diazepam

MOA: pr***omote & facilitate central vestibular compensation via GABA modulation***

Drugs that have ANTIEMETIC effect

Note: When vestibular nerve is stimulated it send signals to brain (chemoreceptor trigger zone in the area of postrema) _it will induce nausea ,vomiting > the vestibular suppressant drugs act as antiemetic and suppress this impulses and the mediator that cause this condition **(dopamine+ histamine)**

H1 antagonist :

a) Antihistamine : Meclizine
b) Anticholinergic **: Dimenhydrinate** *(the most important)*

Note:
Dimenhydrinate is :

- *more effective in vertigo than meclizine*
- *it is the commonest drug to* ***prevent motion sickness***

1-DIMENHYDRINATE (Dramamine) :

-antihistamine (Block H1 receptors in CRTZ)
- weak anticholinergic effects
-sedative effect
-More antiemetic effect less sedating effect than Meclizine

Indications:

1. in vertigo
2. **In control of MOTION SICKNESS by** ↓ excitability in the labyrinth & blocking conduction in vestibular-cerebellar pathways.

ADRs:

- Sedation
- **Dizziness**
- Anticholinergic side effects:

In kids : flushing + dehydration

In old age : glaucoma + prostate hyper atrophy

Contraindications:

1. Glaucoma (Anticholinergic affect will increase intraocular pressure)
2. Prostatic enlargement (Anticholinergic affect will cause contraction of the sphincter that will make the condition worse)

* it Can be substituted by Meclizine

---

2) Phenothiazines- -have these characters :

- Dopamine antagonists + Sedation
- Examples:
- Prochlorperazine
- Promethazine (less sedation **so Prochlorperazine is better because it has more sedative effect)**

PROCHLORPERAZINE - A Piperazine Phenothiazines (better choice) :

- Block dopamine receptors at CRTZ
- Antipsychotic (treatment of schizophrenia)+some sedation + antiemetic

Indications:

- One of the best antiemetics in vertigo
- sedating & has some vestibular suppressant action

---

3) Dopamine Antagonists *(in migrane + GIT):*

a) Dopamine Antagonist

b) Gastroprokinetic *(rabidly provoke the stomach so there is nothing to be evacuated and that will reduce the sense of nausea + vomiting-)*

Examples:

Metoclopramide *(it has many side effects but it cross the BBB so it better)* **Domperidone ➜** *which is not used because it doesn't cross BBB*

Note:

Metoclopramide is pure dopamine antagonist _ (differs from phenothiazine drugs)_so it is not used as a treatment of schizophrenia

METOCLOPRAMIDE

- Dopamine Antagonists
- A potent central antiemetic acting on CRTZ
- Has some sedating action
- Has potent gastroprokinetic effect

Indications:

In vertigo

ADRs

1. Restlessness or drowsiness
2. Extrapyramidal manifestations on prolonged use *(Parkinson like effect)=because of low dopamine level*

DRUGS INDUCING VERTIGO

Are those drugs (or chemicals) producing destructive damaging effects on structure or function of labyrinthine hair cells &/ or their neuronal connections

1. VESTIBULOTOXINS

There are group of drugs that effect the function of labyrinth (the vestibule only) and induce vertigo (no loss of hearing)

They are mainly two types:

a- Drugs altering fluid & electrolyte

- Diuretics
- Antihypertensive....

B-Drugs altering vestibular firing:

- Anticonvulsants
- Antidepressants
- Sedative hypnotics
- Alcohol
- Cocaine

2. MIXED OTOTOXINS??

Drugs that effects the structures and functions of the labyrinth (vestibule +cochlea together) and cause vertigo + impairment or loss of hearing

- **Aminoglycoside antibiotics:**

(gentamycin ,kanamycin ,neomycin , streptomycin , tobramycin , netlimycine)

- Fluroquinolines, Vancomycin, Polymixin
- Quinine, chloroquine, quinidine
- Nitrogen mustard
- Loop diuretics
- NSAIDs
- Tobacco

** Note*

Amino glycoside antibiotic cause structural changes in the labyrinth result **otitis and tinnitus:**

- **Neomycin** → **activate caspases** (which is important to perform the apoptosis procedure) → Death Receptor Pathway
- **Gentamycin** → **evoke free radicals** → Mitochondrial Pathway (damage to the mitochondria)

These ototoxic drugs cause **functional change:**

- Quinine, chloroquine, quinidine
- Loop diuretics
- NSAIDs

Firing of impulses→⇓ local blood flow → biochemical changes

→ alter electromechanical transduction

N.B:

1. **Betahistine (the first choice to reduce spinning) .>>Pheocromocytoma , Bronchial asthma are contraindicated because increasing level of histamine**
2. **Dimenhydrinate is the first choice to treat pt with motion sickness also it's effective in vertigo however it may cause dizziness as ADRs**
3. **Glaucoma and prostate hypertrophy ARE contraindicated in dimenhydrinate so we can use meclizine instead of it**
4. **PROCHLORPERAZINE is suitable as antiemetic in patient with schizophrenia**
5. **Don't use METOCLOPRAMIDE in prolonge used to be away from parkinsonism _choose another drug in case OF prolong use**
6. **VESTIBULOTOXINS are the drugs that effect the function of vestibule mainly**
7. **Ototoxin are the drugs that effect the function and structure of vestibule and cochlea**
8. **aminoglycoside antibiotic cause structural changes in the labyrinth result otitis and tintus:**
   - **Neomycin → activate caspases (which is important to perform the apoptosis procedure) → Death Receptor Pathway**
   - **Gentamycin → evoke free radicals → Mitochondrial Pathway (damage to the mitochondria)**
9. **ototoxic drugs cause functional change:**
   - **Quinine, chloroquine, quinidine**
   - **Loop diuretics**
   - **NSAIDs**

   Firing of impulses→ local blood flow → biochemical changes
   → alter electromechanical transduction