Pharmacology Team 431

(CNS BLOCK)

Drugs Affecting Balance System

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GREEN: doctors explanation
BLUE: additional
RED: very important
GREY: not important
Other than that is just a format

THERAPEUTIC MANAGEMENT

1- Prevent Recurrence:

Intend to suppress acute attacks [tame vertigo episodes]:

a) Diuretics (↓fluid retention) (not loop diuretics B/C their main side effects are: Vertigo + autotoxicity eg: **furosemide"**

(used with high pressure, congestion, or premenstrual "if she predisposed to get vertigo attack before period")

b) Corticosteroids (↓inflammation)

"eg: fluid retention causes inflammation and this will alter the hair cells function"

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

"to shunt the load and adjust it between the perilymph and endolymph"

eg:cinnarazine, flunnarazine and **verapamil** "b/c they are selective vasodilators of the brain"

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

2- Vestibular Suppressants:

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

↓Spinning + ↓Emesis "vomiting"

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

VESTIBULAR SUPRESSANTS "ANTIEMETICS"

1)H1 antagonist:

a) Antihistamine: Meclizine

b) Anticholinergic: **Dimenhydrinate (Dramamine)**:

-Antihistamine(Block H1 receptors in CRTZ)"CRTZ=Chemoreceptor Trigger Zone"

- Weak anticholinergic effects

-Sedative effect

-More antiemetic effect less sedating effect than Meclizine "more effective in vertigo than meclizine"

Indications:

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

ADRs:

- Sedation - Dizziness
- Anticholinergic side effects

(kids : flushing + dehydration, old age: glaucoma + prostate hyper atrophy)

Contraindications:

1. Glaucoma (Anticholinergic affect will increase intraocular pressure)
2. Prostatic enlargement

2) Phenothiazines:

Dopamine antagonists "non selective"+ Sedation

a) **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

b) Promethazine (less sedation so Prochlorperazine is better because it has more sedative effect b/c some attacks stayes for hours to days so the patint must be sedated to avoid any injury)

3) Dopamine Antagonists "selective":

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

a) **Domperidone** ➔ *not used because it doesn't cross BB*
b) **Metoclopramide** *(it cross the BBB so it better "not for chronic use due to its harmful side effects)*
- 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"*

VESTIBULAR SUPRESSANTS "Drugs⬇Spinning"

1) ***H1 agonists + H3 antagonists***: **Betahistine (the first choice)**

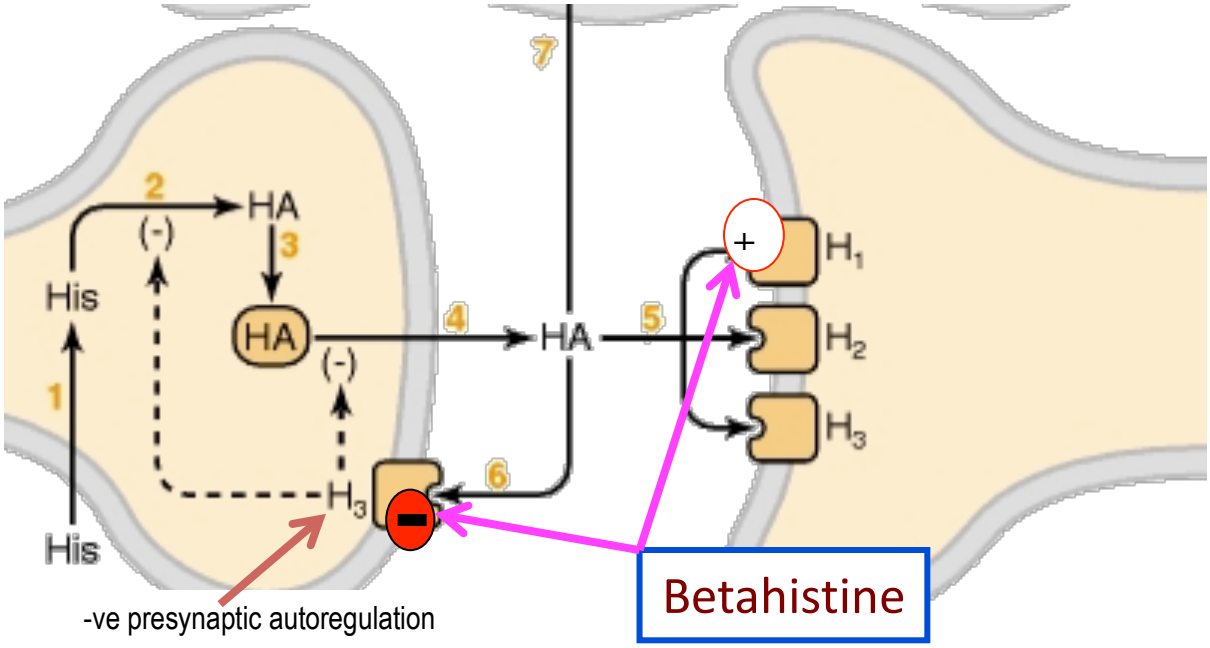
2) ***Benzodiazepines:*** promote & facilitate central vestibular compensation via GABA modulation
e.g.: Lorazepam - Clonazepam - Diazepam
It's used only if the H1 + H3 antagonist failed

1) Betahistine (the best medication for spinning):

1) Weak agonist at H_1 receptors → regulates inner ear fluid homeostasis (labyrinthine circulation) → inducing vaso-dilatation in middle ear but not inner ear → 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.



Pharmacokinetics (not imp):

1. Tablet form , rapidly & completely absorbed
2. t.=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**
2. **Pheocromocytoma** *(benign tumor of the adrenal medulla , histamine plays a role in progression of this disease)*
3. **Bronchial asthma**

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

They are group of drugs that effect the function of labyrinth (the vestibule only) and induce vertigo (no loss of hearing) "mostly functional changes"

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

A: structural derangement:

- **Aminoglycoside antibiotics:**

(Gentamycin ,Kanamycin ,Neomycin , Streptomycin , Tobramycin , Netlimycine)

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

B: **Functional Changes:**

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

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

Questions

1) Sara, 40 years old female noticed that she gets a virtigo for the day before her period for the last 4 months. the doctor prescribed her a drug to prevent futher primenustrual virtigo. The drug is:
   A) Furosemide
   B) Cinnarazine
   C) Meclizine

2) Abdullah, 50 years old male. He is traveling from Jeddah to Egypt by ferry and suddenly he feel nauseous and dizzy. Which one of the folowing can stop his symptoms:
   A) Dimenhydrinate
   B) Betahistine
   C) Quinine

3) **Neomycin can promote apoptosis by:**
   A) Activating caspases
   B) Evoking free radicals
   C) Both A & B