

Neuropsychiatry Block

Pharmacology Team 439

Medications Affecting The Balance System

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

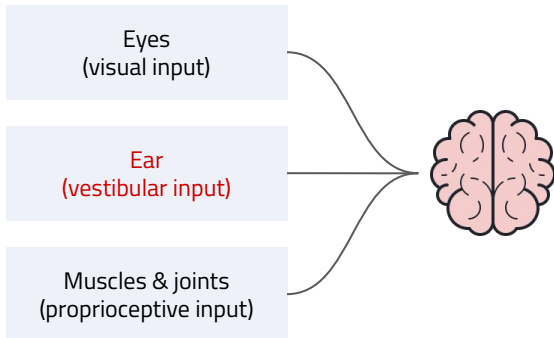
Extra

Objectives:

- 1-Differentiate between classes of drugs used to control or prevent vertigo.
- 2-Hint on some disorders of balance.
- 3-Details on some drugs used to control or prevent vertigo.
- 4-Identify drugs that can precipitate vertigo.

Introduction

Balance System



Is the system that prevent humans and from falling over when standing or moving, and it results from number of body systems working together.

Vestibular component of balance is primarily controlled by structure in our inner ear called the **labyrinth** filled with fluid (**endolymph**). Upon movement, fluid in the semi-circular canals stimulates nerve endings → firing impulses along the vestibular nerve to the brain.

If a disease or injury damages this system, it can lead to a vestibular disorder causing vertigo and dizziness.

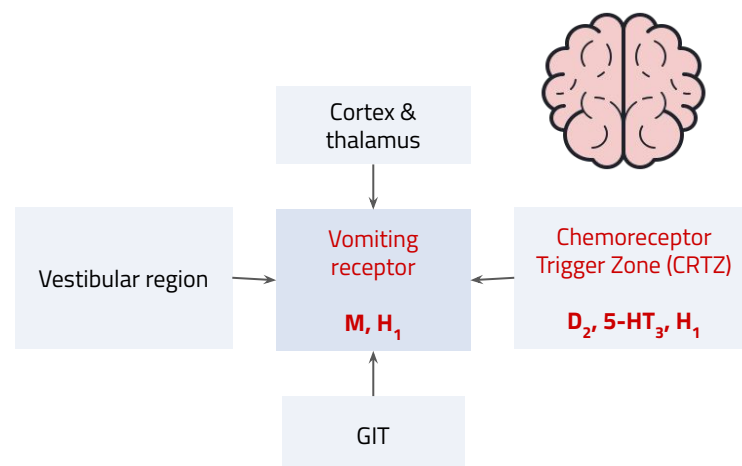
Nausea & Vomiting

- Vomiting or emesis, is the forceful expulsion of gastrointestinal contents through the mouth.
- The vomiting center lies in the medulla oblongata and comprises the reticular formation and the nucleus of the tractus solitarius. When activated, motor pathways descend from this center and trigger GIT muscles for vomiting.
- The vomiting center can be activated directly by irritants or indirectly following input from 4 principal areas:

- 1- Gastrointestinal tract
- 2- Cerebral cortex and thalamus
- 3- Vestibular region
- 4- **ChemoReceptor Trigger Zone (CRTZ)**

The chemoreceptor trigger zone (CRTZ), is located within the dorsal surface of the medulla oblongata, on the floor the fourth ventricle of the brain.

The CRTZ contains receptors that detect emetic agents in the blood and upon stimulation, it relays that information to the vomiting center which is responsible for inducing the vomiting reflex.



Antiemetic drugs that will be discussed in this lecture will block these receptors to inhibit vomiting & nausea.

Terms Related to Balance

Dizziness/Lightheadedness:

Used to express subjective patient complaints related to changes in sensation, movement, perception, or consciousness.

Vertigo:

Type of dizziness described as the sensation that the environment is spinning.

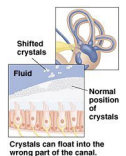
Symptoms of vertigo:	<ul style="list-style-type: none"> - Spinning (vertigo). - Confusion or disorientation. (loss of sense of direction & position) - Falling, or feeling as if one is going to fall. - Nausea or vomiting. - Sweating. - Abnormal eye movement (Nystagmus), repetitive uncontrolled movements.
Patho-physiology	Vestibular system is responsible for our balance, and If this system is disturbed or damaged by disease, aging, injury, or simply confused neuronal input, vestibular disorders will result with symptoms such as vertigo and dizziness..
Types:	<p>1- Objective: objects are moving while the patient is stationary.</p> <p>2- Subjective: patient is moving while surroundings are stationary.</p>

Balance Disorders:

1

Benign paroxysmal positional vertigo (BPPV):

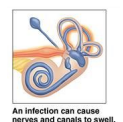
A **change in head position** causes a sudden sensation of spinning.



2

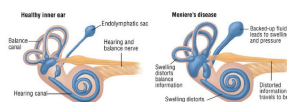
Acute labyrinthitis:

Inflammation of the balance apparatus of the inner ear, probably caused by a viral infection.



3

Ménière disease:



A disorder of the inner ear, which causes repeated episodes of dizziness, usually with ringing in the ear & progressive low-frequency hearing loss.

This disorder results from edema and increased pressure in endolymphatic sac of inner ear, thus it is also called "**Endolymphatic hydrops**" it's **NOT** affected by head position

Overview

Drugs related to Balance System

Prophylactic Treatment

Aims to reduce the recurrence of specific vertiginous conditions. E.g:

1- **Diuretics** (but NOT loop diuretics). → as described earlier, some disorders caused by edema such as meniere's disease, and diuretics might be helpful in this case. But why not loop diuretics? Because if you recall from renal block, **ototoxicity** was the most common adverse effect of loop diuretics.

2- **Ca & K Channel Blocker & Antihistamine** e.g. Cinnarizine & **verapamil**.
The blockage of these channels reduce the kinetic activity & hydrostatic pressure on the hair cells.
(Cinnarizine blocks both Ca and K channel while verapamil blocks Ca channel only).

3- **Corticosteroids**. Can relieve the edema by their anti-inflammatory effect.

Specific Treatment

Involves targeting the underlying cause of the vertigo (e.g., ear infection)

By usage of **antibiotics, antivirals, and anti-inflammatory drugs.**

Symptomatic Treatment

Balance disorders are not treatable, so our intervention only involves controlling the acute symptoms & autonomic complains such as vertigo and vomiting. By usage of:

1. Vestibular Suppressants

Reduce the intensity of **vertigo** and **nystagmus** evoked by vestibular imbalance

Drugs:

1- **Anticholinergic:**
hyoscine

2- **Benzodiazepine:**
lorazepam -clonazepam -diazepam

3- **Betahistine**

2. Antiemetics

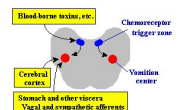
Used to control **vomiting** and **nausea**

Drugs:

1- **Antihistamine:**
dimenhydrinate

2- **Phenothiazine:**
prochlorperazine

3- **Dopamine antagonists:**
metoclopramide -domperidone



1. Vestibular Suppressants

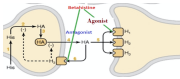
Anticholinergics

Drug	Hyoscine aka Scopolamine* (*Dr: "another name add it to your slides")
Action	<ul style="list-style-type: none"> - Inhibits firing in vestibular nucleus neurons (suppresses the electrical activity & conduction of impulses from the vestibule to the vestibular nucleus and higher centers) - Reduce the velocity of vestibular nystagmus (uncontrolled eye movement)
Indications	<ol style="list-style-type: none"> 1- Motion sickness 2- Sedation
Adverse effects	- Dry mouth, blurred vision, and sedation.


Benzodiazepines

Drug	Lorazepam, Clonazepam, Diazepam
Action	Enhancing the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABAA receptor, resulting in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant properties.
Indications	<ul style="list-style-type: none"> - Management of acute vertigo (in small doses). Toxicity in large doses - Minimize anxiety and panic associated with vertigo
Adverse effects	<ul style="list-style-type: none"> - Dependence, and impaired memory. If used for more than 2 weeks. - Increased risk of falling (Ataxia). due to muscle relaxation.

Betahistine

M.O.A	<p>It's a structural analog of histamine which works as: </p> <p>H₁ agonist, H₃ antagonist, and increases serotonin</p> <ol style="list-style-type: none"> 1- Weak H₁ receptor agonist: stimulating the H₁ receptors in the inner ear → local vasodilatory effect and increased permeability in the blood vessels → helps to reverse the underlying problem of endolymphatic hydrops. 2- More potent H₃ receptor antagonist/blocker: Increases the local concentration of histamine in the inner ear. (enhances the H₁ agonist activity) <small>H₃ is an inhibitory presynaptic receptors that inhibit histamine release and works as a negative feedback mechanism. In short: - Stimulating H₃ → Less histamine is released → less histamine to act on H₁ receptor = no vasodilation & increased endolymphatic pressure ❌ - Blocking H₃ → More histamine is released → more histamine to act on H₁ receptor = vasodilation & reduced endolymphatic pressure ✓</small> 3- Increases the level of serotonin in the brainstem which decreases the activity of vestibular nuclei (goal).
P.K	<ol style="list-style-type: none"> 1- Formulated as tablets or oral solution 2- Rapidly and completely absorbed 3- T_{1/2} is 3-4 hours & low protein binding 4- Excreted in urine within 24 hours
Indications	Ménière's syndrome (Although current evidence is limited as to whether betahistine prevents vertigo attacks caused by Ménière's disease, compared with placebo reactions. In the USA its effect is thought to be no better than a placebo). You can find the trial here
Adverse effects	<ul style="list-style-type: none"> - Headache (due to dilation of vessels), and nausea (due to stimulation of CRTZ). - GIT side effects (Inc. of HCl), & hypersensitivity reaction.
Contraindications	<ul style="list-style-type: none"> - Pheochromocytoma (because it increases adrenaline secretion → hypertensive crisis) - Bronchial asthma. (due to bronchoconstriction) <p>Remember that H₁ receptor: (in smooth muscle: contraction) (in blood vessel: dilation & increased permeability).</p> <ul style="list-style-type: none"> - History of peptic ulcer (histamine increase HCL release → worsen peptic ulcers) - Hypersensitivity reactions.

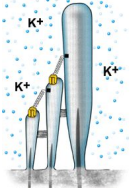
2. Antiemetics

Antihistamines	
Drug	Dimenhydrinate
M.O.A	<ol style="list-style-type: none"> 1- Block H₁ receptor in CRTZ (chemoreceptors trigger zone) vomiting center 2- Sedative effect histamine is responsible for wakefulness in the brain, blocking its receptors → sedative effect 3- Weak anticholinergic effect causes vestibular suppression 4- ↓ excitability in the labyrinth and blocks conduction in the vestibular-cerebellar pathways (slows the impulses from vestibule to vestibular nucleus).
Indications	<ul style="list-style-type: none"> - Vertigo - Prevention of nausea & vomiting associated motion sickness
Adverse effects	- Sedation, dizziness, & anticholinergic* side effects *with chronic use
Contraindications	<ul style="list-style-type: none"> - Glaucoma due to anticholinergic effects, it blocks the muscarinic receptor → relaxes sphincter pupillae muscle → inhibit outflow of aqueous humor - Prostatic enlargement relaxes bladder wall, blocks sphincter → urinary retention 

Phenothiazines	
Drug	Prochlorperazine
M.O.A	<ol style="list-style-type: none"> 1- Blocks Dopamine receptors at CRTZ (chemoreceptors trigger zone) 2- Antipsychotic with some sedation 3- Antiemetic 4- Some vestibular suppressant action
Indications	One of the best antiemetic drugs used in vertigo

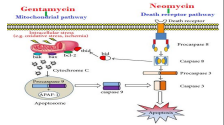
Dopamine Antagonists	
Drugs	Metoclopramide & Domperidone (D ₂ Antagonists)
M.O.A	<ol style="list-style-type: none"> 1- Block DOPAMINE D₂ receptors in the CRTZ of the medulla, resulting in potent central antinausea & antiemetic action. 2- Some sedative action. 3- Potent gastroprokinetic effect. strengthen lower esophageal sphincter → increase stomach contraction → prevents acid reflux and promote gastric emptying and motility → prevent further pressure toward vomiting.
Indications	Gastroesophageal Reflux Disease (GERD) increase gastric acid emptying which will control gastric acid reflux.
Adverse effects	<ul style="list-style-type: none"> - Restlessness or drowsiness - Extrapyramidal manifestations on prolonged use. tremors and muscle rigidity, and parkinson's like syndrome (because it affects extrapyramidal system "substantia nigra" which also has dopamine 2 receptors)

Prophylactic Treatment

Calcium Channel Blockers	
Drug	Cinnarizine
M.O.A	<p>1- Selective K^+ & Ca^{2+} channels blockers (vascular smooth muscle relaxation).</p> <p>2- Antihistamine, Antiserotonin, Antidopamine <i>vasodilation in smc</i></p> <p>3- Promotes cerebral blood flow <i>improves memory</i></p> <p>4- Inhibits K^+ currents i.e. K^+ currents are generated by increased hydrostatic pressure on hair cells, inhibition of these currents reduces vertigo and motion induced nausea by dampening the over-reactivity of the vestibular hair cells</p> 
P.K.	<p>1- Taken orally in tablet form</p> <ul style="list-style-type: none"> - Low oral bioavailability due to hepatic first pass metabolism - Better bioavailability if administered as IV lipid emulsions <i>(simply adding lipids into the drug → increase lipophilicity → better bioavailability)</i> <p>2- Rapidly absorbed.</p>
Clinical uses (Prophylactic)	Nausea & vomiting associated with motion sickness, vertigo, meniere's disease.
Contraindications	Parkinsonism / Car drivers (antihistaminic)
Adverse effects	Sweating, headache, drowsiness, and muscle rigidity and tremors.

Drugs Inducing Vertigo

Drugs producing damaging effects on structure or function of labyrinthine hair cells &/or their neuronal connections.

A- Vestibular toxins	Altering function	<p>1- Drugs altering fluid and electrolyte balance:</p> <ul style="list-style-type: none"> - Diuretics <p>2- Drugs altering vestibular firing (neuronal depressant):</p> <ul style="list-style-type: none"> - Anticonvulsants - Antidepressants - Sedative hypnotics - Alcohol - Cocaine
B- Mixed ototoxins	Altering structure	<p>Aminoglycosides antibiotics:</p> <ul style="list-style-type: none"> - GentaMycin (induces apoptosis by evoking free radicals → Mitochondrial pathway) <i>first-choice drug</i> - NEomycin (induces apoptosis by activating caspases → DEath receptor pathway) - Kanamycin - Streptomycin 
	Altering function	<ul style="list-style-type: none"> - Quinine, chloroquine, quinidine - Nitrogen mustard - Loop diuretics e.g. Furosemide, Torsemide, Bumetanide, Ethacrynic acid. - NSAIDs - Tobacco <p>They ↓ decrease local blood flow → biochemical changes → ↓ electromechanical transduction → ↓ firing of impulse.</p>

Summary

	Class	Drug	MOA	Indications	ADRs	Contra-indications
Vestibular Suppressants	Anticholinergics	Hyoscine	1- Inhibits firing in vestibular nucleus neurons 2- Reduce the velocity of vestibular nystagmus	Motion sickness & sedation.	Dry mouth, blurred vision, sedation.	
	Benzodiazepines	Lorazepam, Clonazepam, Diazepam		1- Acute vertigo (small doses) 2- Minimize anxiety associated with vertigo	Dependence, impaired memory, increased risk of falling (ataxia)	
	Betahistine	Betahistine	1- H ₁ agonist (vasodilation) 2- H ₃ antagonist (increase histamine) 3- increase serotonin	Ménière's syndrome	Headache, GIT disturbance, hypersensitivity	Pheochromocytoma asthma, peptic ulcer, hypersensitivity
Antiemetics	Antihistamines	Dimenhydrinate	1- Block H ₁ receptor in CRTZ 2- Sedative effect 3- Weak anticholinergic effect 4- Decreases excitability in the labyrinth & blocks conduction in the vestibular-cerebellar pathways	Vertigo & motion sickness	Sedation, dizziness	Glaucoma Prostatic enlargement
	Phenothiazines	Prochlorperazine	1- Blocks Dopamine receptors at CRTZ 2- Antipsychotic 3-Antiemetic 4- Vestibular suppressant action	Vertigo (BEST)		
	Dopamine Antagonists	Metoclopramide	1- Block DOPAMINE D ₂ receptors in the CRTZ 2- Sedation 3- Potent gastroprokinetic effect	GERD	Restlessness, drowsiness, Extrapyramidal manifestations	
Prophylactic	Calcium Channel Blockers	Cinnarizine	1- Selective K ⁺ & Ca ²⁺ channels blockers 2-Antihistamine, Antiserotonin, Antidopamine 3-Promotes cerebral blood flow 3-Inhibits K ⁺ currents	Prophylactic cases motion sickness, vertigo, meniere's disease.	Sweating, headache, drowsiness, and muscle rigidity and tremors.	Parkinsonism Car drivers

MCQs

Click [here](#) for some amazing quizlet flashcards done by Nouf Alsubaie

Q1: Neomycin induces apoptosis through:			
A- The intrinsic pathway	B- Mitochondrial pathway	C- Biochemical changes	D- Death receptor pathway
Q2: A 42 years old lady is having a yacht tour the Red Sea, and suddenly she feels nauseous and dizzy. Which one of the following can stop her symptoms?			
A- Betahistine	B- Domperidone	C- Dimenhydrinate	D- Metoclopramide
Q3: A 56 years old male came to the hospital complaining of repeated episodes of dizziness, usually with ringing in the ear & progressive low-frequency hearing loss. His doctor diagnosed him with an inner ear disorder called Meniere's disease. Which one of the following should be prescribed?			
A- Betahistine	B- Dimenhydrinate	C- Hyoscine	D- Metoclopramide
Q4: A 31 years old women was diagnosed with balance disorder, and a suitable symptomatic treatment drug was prescribed along with a prophylactic one. After a while, she came back complaining of excessive sweating and rigidity in her muscles. Which one of the following might be the causative drug for her complains?			
A- Betahistine	B- Dimenhydrinate	C- Cinnarizine	D- Hyoscine
Q5: Which type of these diuretics is functional ototoxin?			
A- Thiazide diuretics	B- K-sparing diuretics	C- Loop diuretics	D- Carbonic anhydrase inhibitors
Q6: Which one of the following drugs is contraindicated in Pheochromocytoma?			
A- Betahistine	B- Dimenhydrinate	C- Hyoscine	D- Cinnarizine
Q7: Which one of the following drugs is contraindicated in Parkinsonism?			
A- Betahistine	B- Dimenhydrinate	C- Hyoscine	D- Cinnarizine
Q8: Prochlorperazine is one of the best antiemetic drugs used in vertigo. Which one of the following is its true M.O.A?			
A- Block H ₁ receptor in CRTZ	B- Blocks Dopamine receptors at CRTZ	C- Block Dopamine D ₂ receptors in the CRTZ of the medulla	D- H ₃ receptor antagonism

1	2	3	4	5	6	7	8
D	C	A	C	C	A	D	B

SAQ

Q1) Drugs inducing vertigo divided into two groups, name them and give an example for each group?

Q2) Name a dopamine antagonist, describe its M.O.A, indication, and adverse effects.

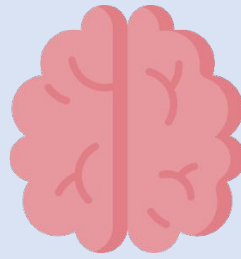
Answers

A1) [Slide 7](#)

A2) [Slide 6](#)



Feedback Form



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