

Medication affecting the balance system

- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE



Objectives



Differentiate between classes of drugs used to control or prevent vertigo.



Hint on some disorders of balance.



Details on some drugs used to control or prevent vertigo.



Identify drugs that can precipitate vertigo.



Introduction

Balance System

- Is the system that prevent humans 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.

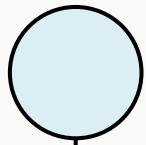
The vomiting center lies in the medulla oblongata and comprises the reticular formation and the nucleus of the tractus solitarius. When activated, motor pathways descend from this center and trigger GIT muscles for vomiting.

The vomiting center can be activated directly by irritants or indirectly following input from 4 principal areas:

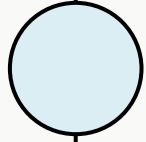
- 1- Gastrointestinal tract
- 2- Cerebral cortex and thalamus
- 3- Vestibular region
- 4- ChemoReceptor Trigger Zone (CRTZ)

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.

Terms Related to Balance system



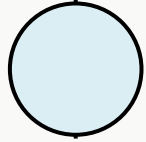
Dizziness & Lightheadedness: To express subjective patient complaints related to changes in sensation movement, perception, or consciousness



Vertigo:

Symptoms of vertigo:

- Spinning (vertigo).
- Confusion or disorientation. (loss of sense of direction & position)
- Falling, or feeling as if one is going to fall.
- Autonomic dysfunction:** Nausea & vomiting, Sweating.
- Abnormal eye movement (Nystagmus)



Ménière's disease

Epidemiology of Balance system

01

The overall incidence of dizziness, vertigo & imbalance is
(5-10%)/(15-20%)

02

It reaches 40% in patients older than 40 years

03

Accounts for 3% of total visits to emergency department

04

The incidence of falling is 25% in subjects older than 65 years

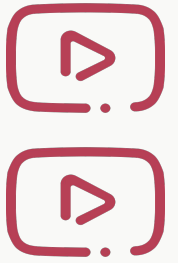
05

1% of falls results in hip fracture

06

Roughly 50% of fractured hips will not function normally.

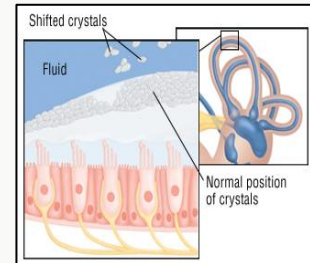
Balance Disorders



1

Benign paroxysmal positional vertigo (BPPV):

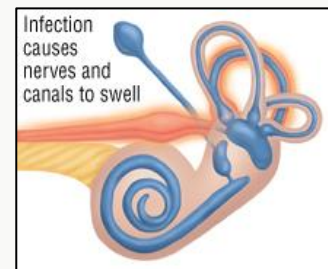
A change in head position causes a sudden sensation of spinning. **Due to crystal shifting**



2

Acute labyrinthitis:

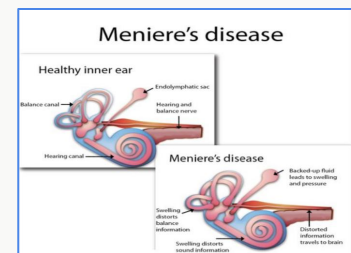
Inflammation of the balance apparatus of the inner ear, probably caused by a viral infection.



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 **“If left untreated”**.



Drugs Related to Balance

01 Prophylactic treatment

Aims to reduce the recurrence of specific vertiginous conditions.

1- Diuretics (except loop diuretics)

-ototoxicity is the most common adverse effect of loop diuretics.

Cuz Inner ear has Na⁺/K⁺/Cl⁻ cotransporter which is the same transporter in the ascending loop of Henle. And the function of loop diuretics is blocking this transporter.

2- Ca & K Channel Blocker & Antihistamine.

e.g. Cinnarizine : Antihistamine & blocks both Ca and K channels. The blockage of these channels reduces the kinetic activity & hydrostatic pressure on the hair cells.

3-Corticosteroids.

Can relieve the edema by their anti-inflammatory effect.

02 Specific treatment

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

By usage of antibiotics, antivirals, and anti inflammatory drugs (avoid ototoxic drugs)

03 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:

Vestibular Suppressants

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

Drugs: 1- Anticholinergic:

Hyoscine

2- Benzodiazepine:

Lorazepam, Clonazepam,

Diazepam

3- Betahistine

Antiemetics

Used to control vomiting and nausea

Drugs:

1- Antihistamine: Dimenhydrinate

2- Phenothiazine:

Prochlorperazine

3- Dopamine antagonists:

Metoclopramide & Domperidone

Vestibular Suppressants

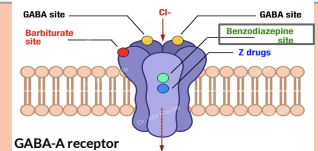
Anticholinergic

Prototype: Atropine

Drugs	MOA	Indication	ADRs
<p>Hyoscine aka Scopolamine*</p>	<p>All of the vestibular system is supplied by cholinergic system, so anticholinergics will:</p> <ul style="list-style-type: none"> - Inhibit firing in vestibular nucleus neurons - Reduce the velocity of vestibular nystagmus (uncontrolled eye movement) 	<p>Useful in motion sickness and sedation.</p>	<ul style="list-style-type: none"> - Dry mouth, blurred vision, and sedation. <p>Atropine like ADRs</p>

Benzodiazepines

Prototype: Diazepam



Drugs	MOA	Indication	ADRs
<p>Lorazepam, Clonazepam, Diazepam</p>	<p>Enhancing the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABA receptor, resulting in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant properties.</p>	<ul style="list-style-type: none"> - Useful in management of acute vertigo (in small doses). - Minimize anxiety and panic associated with vertigo. - Benzodiazepines are mainly Anti - seizure drugs 	<ul style="list-style-type: none"> - Dependence, and impaired memory. <p>Dependence is caused since they are hypnotics, the patient will have difficulties in effects sleeping if the drug was taken in high doses & then stopped suddenly.</p> <ul style="list-style-type: none"> - Increased risk of falling because it causes relaxation of muscle.

Vestibular Suppressants

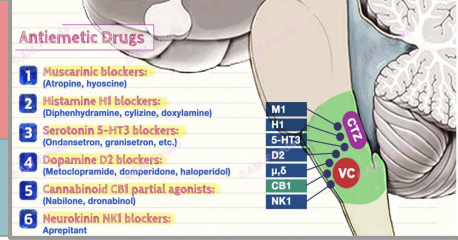


Drug: Betahistine

<p>MOA</p>	<p>It's a structural analog of histamine which works as: H1 agonist, H3 antagonist, and increases serotonin. It has several MOA, the main goal is to:</p> <ul style="list-style-type: none"> -increase histamine locally -> vasodilation -> fluid drainage -increase serotonin in the vestibular nuclei-> vestibular suppression <p>1- Weak H1 receptor agonist: stimulating the H1 receptors located on blood vessels in the inner ear → local vasodilation & increased permeability → which helps to reverse the underlying problem of endolymphatic hydrops “Ménière’s disease”</p> <p>2-More potent H3 receptor antagonist properties: By blocking H3 receptors, increases the local concentration of histamine in the inner ear. H3 is an inhibitory presynaptic receptors that inhibit histamine release and works as a negative feedback mechanism</p> <p>3-increase serotonin levels in the brain stem which decreases the activity of vestibular nuclei</p>	
<p>P.K</p>	<ol style="list-style-type: none"> 1- Formulated as tablets or oral solution 2- Rapidly and completely absorbed 3- T1/2 is 3-4 hours & low protein binding 4- Excreted in urine within 24 hours 	
<p>Clinical Indication</p>	<p>Treatment of Ménière’s syndrome efficacy and safety of betahistine treatment in patients with Meniere’s disease: primary results of a long term, multicentre, double blind, randomised, placebo controlled, dose defining trial (BEMED trial) BMJ 2016; 352 (Although current evidence is limited as to whether betahistine prevents vertigo attacks caused by Ménière’s disease, compared with placebo reactions.) 94% of ENT surgeons in Britain prescribe betahistine for Meniere’ disease, while in USA they think it is no better than a placebo.</p>	
<p>ADRs</p>	<ul style="list-style-type: none"> - Headache (due to dilation of vessels) - GIT side effects & nausea 	
<p>C.I</p>	<p>Pheochromocytoma: Adrenal medulla tumor causes high catecholamines, betahistine will also increase catecholamines causing hypertensive crisis</p> <p>2-Bronchial asthma due to bronchoconstriction</p> <ul style="list-style-type: none"> -H1 in smooth muscle: contraction -H1 in blood vessels: dilation & increased permeability <p>3. History of peptic ulcer :increased stomach acidity</p> <p>4. Hypersensitivity reactions.</p>	



Antiemetics



Antihistamines

Drug	Dimenhydrinate 1st generation antihistamine
M.O.A	<p>1- Block H1 receptor in CRTZ (chemoreceptors trigger zone)</p> <p>2- Sedative effect histamine is responsible for wakefulness in the brain, blocking receptors → sedative effect</p> <p>3- Weak anticholinergic effect causes vestibular suppression</p> <p>4- ↓ Excitability in the labyrinth and blocking conduction in the vestibular-cerebellar pathways</p> <p>They have an advantage of blocking both Histamine & Cholinergic effects (antiemetic & vestibular suppressant)</p>
Indications	<p>-Vertigo</p> <p>-Prevention of nausea & vomiting associated motion sickness</p>
ADRs	-Sedation, dizziness, & anticholinergic side effects
C.I	<p>-Glaucoma</p> <p>-Prostatic enlargement Relaxes bladder wall, blocks sphincter → urinary retention “anticholinergic ADR”</p>

Phenothiazines

Drug	Prochlorperazine
M.O.A	<p>1- Blocks Dopamine receptors at CRTZ</p> <p>2- Antipsychotic with some sedation + Antiemetic.</p> <p>3- Some vestibular suppressant action</p>
Indication	One of the best antiemetic drugs used in vertigo

Dopamine Antagonists

Drug	Metoclopramide & Domperidone
M.O.A	<p>1- Block Dopamine D2 receptors in the CRTZ of the medulla, resulting in potent central antinausea & antiemetic action.</p> <p>2- Some sedative action.</p> <p>3- Potent gastroprokinetic effect.</p> <p>increase stomach contraction → prevents acid reflux by promoting gastric emptying and motility → no further pressure toward vomiting.</p>
ADRs	<p>- Restlessness or drowsiness</p> <p>- Extrapyramidal manifestations on prolonged use.</p> <p>-Tremors,muscle rigidity,</p> <p>-Parkinson’s like syndrome : Patients with Parkinson’s have low dopamine, these drugs further affect extrapyramidal system “substantia nigra” which is rich in dopamine 2 receptors)</p>

Prophylactic Treatment



Calcium Channel Blockers

Drug	Cinnarizine
MOA	<p>1- Selective Ca²⁺ channels blockers (vascular smooth muscle relaxation).</p> <p>2- Antihistamine, Antiserotonin, Antidopamine vasodilation in smooth muscle cells</p> <p>M.O.A</p> <p>3- Promotes cerebral blood flow</p> <p>4- Inhibits K⁺ currents in inner ear</p> <p>I.e. K⁺ currents are generated by increased hydrostatic pressure on hair cells, inhibition of K⁺ currents lessen the vertigo and motion-induced nausea by dampening the over-reactivity of the vestibular hair cells</p>
PK	<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 (simply adding lipids into the drug → increase lipophilicity → better bioavailability) <p>2- Rapidly absorbed.</p>
Uses	Nausea & vomiting associated with motion sickness, vertigo, meniere's disease.
ADRs	Sweating, headache, drowsiness, and muscle rigidity and tremors.
Important	
C.I	Parkinsonism, Car drivers (antihistaminic)

Drugs inducing vertigo

A- Vestibular toxins

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

Altering function

1- Drugs altering fluid and electrolyte balance:

- Diuretics especially loop diuretics, other Diuretics are prescribed in emergency

2- Drugs altering vestibular firing (neuronal depressant):

- Anticonvulsants
- Antidepressants
- Sedative hypnotics
- Alcohol
- Cocaine

B- Mixed ototoxins

Important

Altering structure

Aminoglycosides antibiotics:

1- Gentamicin

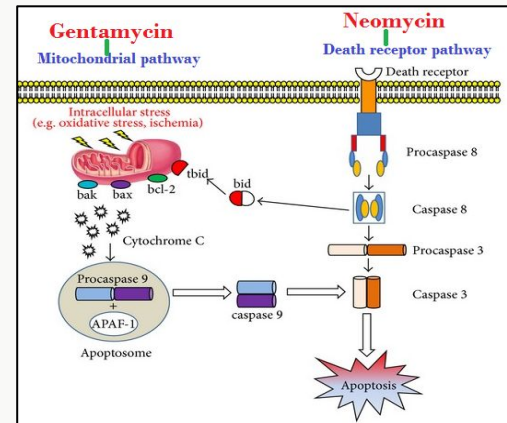
induces apoptosis by evoking free radicals
→ Mitochondrial pathway

2- Neomycin (a shorter pathway)

induces apoptosis by activating caspases
→ Death receptor pathway

3- kanamycin

4- streptomycin



Altering function

They ↓ decrease local blood flow
→ biochemical changes
→ ↓ electromechanical transduction
→ ↓ firing of impulse.

Quinine, chloroquine, quinidine

- Anticancer Drug :Nitrogen mustard
- **Loop diuretics** e.g. Furosemide, Torsemide, Bumetanide,
- NSAIDs
- Tobacco

Summary

	Class	Drug	MOA	Indications	ADRs	#
Vestibular Suppressants	Anticholinergics	Hyoscine	1-Inhibit firing in vestibular nucleus neurons 2 - Reduce the velocity of vestibular nystagmus	1-Motion sickness 2-Sedation.	- Dry mouth, -blurred vision, -sedation.	
	Benzodiazepines	Lorazepam, Clonazepam, Diazepam.	Enhances GABA action on the brain →reduces anxiety associated with vertigo	-Acute vertigo (small doses) -Minimize anxiety and panic associated with vertigo.	-Dependence, and impaired memory. -Increased risk of falling	
	Betahistine	Betahistine	1- Weak H1 agonist (vasodilation) 2- Potent H3 antagonist (increases histamine) 3- Increases serotonin	-Ménière's syndrome	-Headache -Nausea -GIT disturbance	Pheochromocytoma Bronchial asthma History of peptic ulcer hypersensitivity
Antiemetics	Antihistamines	Dimenhydrinate	1- Blocks H1 receptor in CRTZ 2- Sedative effect 3- Weak anticholinergic effect 4- Decreases excitability in the labyrinth & blocks conduction in the vestibular-cerebellar pathways	-Vertigo, Prevention of nausea & vomiting associated motion sickness	-Sedation, -dizziness, - anticholinergic side effects	-Glaucoma -Prostatic enlargement
	Phenothiazines	Prochlorperazine	1-Blocks Dopamine receptors at CRTZ 2-Antiemetic 3-Antipsychotic + sedation 4-Some vestibular suppression	Vertigo		
	Dopamine Antagonists	Domperidone, Metoclopramide	1- Blocks DOPAMINE D2 receptors in the CRTZ of the medulla 2- sedation 3- Potent gastroprokinetic effect		- Restlessness or drowsiness - Extrapyramidal manifestations on prolonged use.	
Prophylactic	Calcium Channel Blockers	Cinnarizine	1- Selective Ca ²⁺ channels blocker 2-Antihistamine, Antiserotonin, Anti dopamine 3-Promotes cerebral blood flow 4-Inhibits K ⁺ currents	Nausea & vomiting associated with motion sickness, vertigo, meniere's disease.	Sweating, headache, drowsiness, and muscle rigidity and tremors.	-Parkinsonism -Car drivers

Summary

Drugs inducing vertigo

Drugs inducing vertigo		
Vestibular toxins	Altering Function	
	1. Drugs altering fluid & electrolyte balance: <ul style="list-style-type: none"> • Diuretics 	2. Drugs altering vestibular firing: <ul style="list-style-type: none"> • Anticonvulsants • Sedative hypnotics • Antidepressants • Alcohol • cocaine
Mixed ototoxins	Altering structure :	Altering Function: ↓local blood flow → biochemical changes → ↓ electromechanical transduction → ↓firing of impulse.
	Aminoglycoside antibiotics : 1- Gentamicin : mitochondrial pathway Induces apoptosis by evoking free radicals 2- Neomycin : death receptor pathway Induces apoptosis by activating caspases	<ul style="list-style-type: none"> • Quinine, chloroquine, quinidine • Nitrogen mustard • Loop diuretics • NSAIDs • Tobacco



MCQ

1. Which of the following is contraindicated in Pheochromocytoma?

A. Betahistine	B. Hyoscine	C. Clonidine	D. Dimenhydrinate
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2. All the following drugs are mixed ototoxins EXCEPT:

A. NSAIDs	B. Quinine	C. Gentamycin	D. Alcohol
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3. Patient come to the ER with vertigo & was diagnosed with Parkinsonism, which of the following drugs will be contraindicated in his case?

A. Cocaine	B. Cinnarizine	C. NSAIDs	D. Neomycin
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4. Which of the following drugs has a potent gastroprokinetic effect ?

A. Domperidone	B. Dimenhydrinate	C. Betahistine	D. Cinnarizine
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5. Which antiemetic also has a weak anticholinergic effect

A. Phenothiazine	B. Metaclopramide	C. Dimperidone	D. Dimenhydrinate
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6. Which Aminoglycoside antibiotics induces apoptosis by evoking free radicals ?

A. Kanamycin	B. Neomycin	C. Gentamycin	D. Streptomycin
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7. All the following are diuretics that could be used to prevent vertigo EXCEPT:

A. Carbonic anhydrase inhibitors	B. K ⁺ sparing diuretics	C. Thiazides	D. Loop diuretics
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SAQ

01

Which Aminoglycoside antibiotics induces apoptosis by activating caspases ?

Neomycin

02

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

Slide 9

03

Which drug is best antiemetic that used in vertigo?

Phenothiazine

04

MOA for betahistine

Slide 8

Team Leaders

Muhannad Al-otabi

Reema Almotairi

Sarah Alajaji

Maryam Alghannam

Team members



Abdulaziz Alamri

Sami Mandoorah

Salma Alkhlassi

Faisal Alateeq

Omar Alamri

Huda bin jadaan

Nazmi M Alqutub

Mohammed Alqutub

Manar Aljanubi

Sultan Almishrafi

Reena Alsadoni

Wasan Alanazi

Mohammed Maashi

Almas Almutairi



Jana Almutlaqah

Mohammed Alasmary

Fatimah Alghamdi

Farah Abukhalaf

Nazmi A Alqutub

Lama Alotaibi

Norah Almalik

Ziad Alhabardi

Salma Alsaadoun

Rawan Alqahtani

Mohammed Alrobeia

Jouri Almaymoni

Aroub Almahmoud

Mohammed Alhudaithi

Faisal alzuhairy

Remaz Almahmoud

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