Lecture 6

Drugs used in parkinsonism

Objectives:

At the end of this lecture you will be able to:-

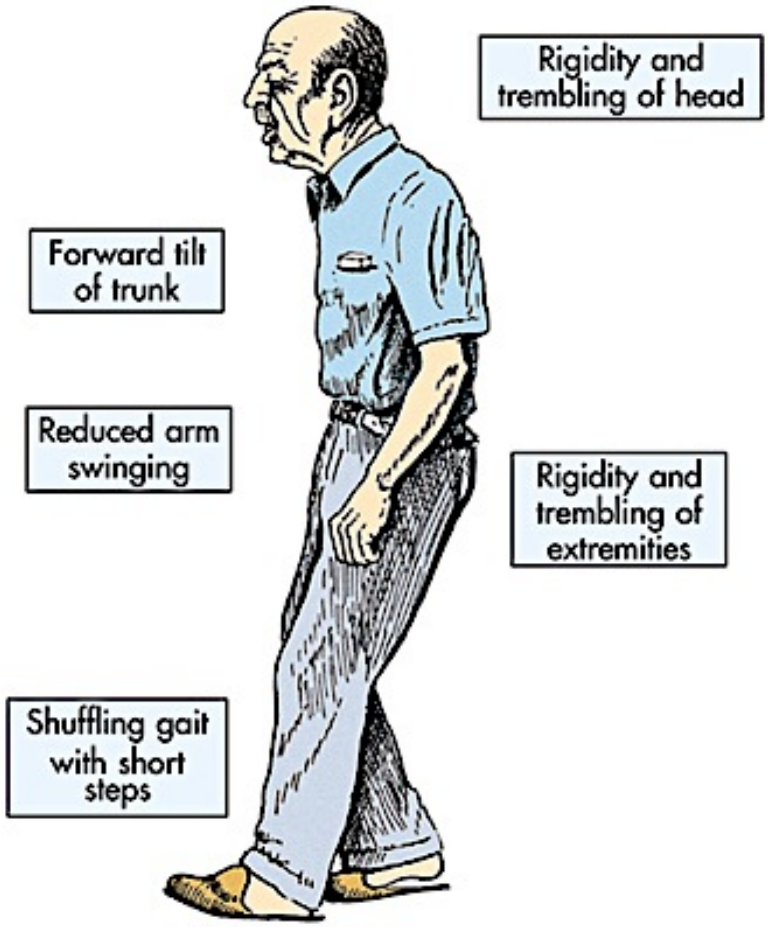
1. Recognize the symptoms and pathophysiology of parkinsonism
2. Understand the pharmacology of drugs used for treatment of parkinsonism.
3. Define pharmacokinetics, pharmacodynamics and side effects of different drugs used for the treatment of parkinsonism.

- Additional Notes
- Important
- Explanation –Extra-

Parkinson's disease:

A progressive neurodegenerative diseases disorder that occurs mainly in the elderly and can lead to disability unless effective treatment is provided.

- Deficiency of dopamine.
- Predominance of Ach.



Pathophysiology of Parkinson's disease:

This movement disorder occurs mainly due to **dopamine/acetylcholine imbalance** (decrease dopamine & increase ACH) in basal ganglia (caudate nucleus, substantia nigra & corpus striatum) that is involved in motor control. (60-90% of dopaminergic receptors are destroyed)

Characters of Parkinson's disease:

simplified by the acronym **"TRAP"**:

- Tremors at rest
- Rigidity of muscles (can't initiate movement)
- Akinesia (no movement) or Bradykinesia (slowness in initiating and carrying out voluntary movements)
- Postural and gait abnormalities
- Anxiety or depression

Causes:

Parkinson's disease is an idiopathic disease but some causes may be:

1. Genetic.
2. Toxins (MPTP= methyl phenyl tetrahydropyridine) (used in animal experiments)
3. Head trauma.
4. Cerebral anoxia .
5. Oxidative stress.
6. Drug-induced Parkinson's disease e.g. **antipsychotics** like **haloperidol** + **Dopamine antagonists** as **metoclopramide** (antiemetic).

Why we don't give Dopamine itself as a treatment?

Because dopamine is polar, it can't cross BBB, so it doesn't cause effect.

MAO-B, COMT & decarboxylase are enzymes that metabolize levodopa peripherally preventing it from crossing BBB.

Drug Treatment

Main approach

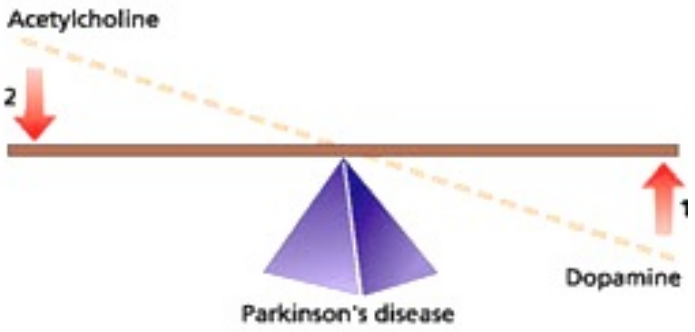
Drugs to increase dopaminergic activity

- Increase central DA synthesis (DA precursors)
  - **L-dopa** + Decarboxylase inhibitor
- Inhibition of DA metabolism
  - **COMT** inhibitors: **Entacapone**, **Tolcapone**
  - **MAO-B** inhibitors: **Selegiline**
- DA receptor agonists
- DA releaser
  - **amantadine** (used as antiviral)

Minor approach

Drugs to block cholinergic activity

- Muscarinic antagonists: **Benzatropine**



Drugs that increase dopaminergic activities

Drug

Increase central DA synthesis (DA precursors) = L-dopa or L-dopa + Decarboxylase inhibitor

Characteristics

Levodopa [L-dopa](non-polar) **:**

- a **precursor** of dopamine
- Levodopa → By dopa decarboxylase (DC) → dopamine [peripherally & centrally]
- Dopamine formed **peripherally** is metabolized by two enzymes: **MAO (**monoamine oxidase**) & COMT (**catechol-o-methyl transferase).
- **99%** L-dopa is **decarboxylated** to give dopamine in **gut** & **liver.**

Because 1% of L-dopa crosses BBB to form dopamine centrally we usually combine it with DC inhibitors to Prevent peripheral conversion of L-dope to dopamine:

- **Carbidopa [only peripheral action cuz its polar]**
- **Benserazide**.
  - ✓ ↓ the effective levodopa **dose**
  - ✓ ↑ **availability** of L-dopa to CNS.
  - ✓ ↓ s**ide effects** of L-dopa.

Pharmaco kinetics

- **Oral** [**taken on empty stomach**] (Eating *proteins* with it interferes with its absorption - have same carrier -)
- Absorbed from **the small intestine** → taken up to CNS by **active** transport system.
- Short duration of action **(t½ =2 h)** → **fluctuation تذبذب of plasma concentration.**
- **Drug Interactions:** High **proteins** meals - Pyridoxine (**Vitamin B6**) (↑ peripheral metabolism) - **Nonselective** MAO inhibitors (**phenelzine**) (no enzymes to metabolize adrenaline → severe vasoconstriction → Hypertensive crisis)

Uses

- **most efficacious** therapy
- best results of levodopa are obtained in the **first few years** of treatment.
- L-dopa ameliorates **all signs** of parkinsonism particularly [**bradykinesia & rigidity**] but does not cure the disease.
  [Shouldn't be used in parkinsonism associated with antipsychotic drug therapy]

Adverse effects

Psychological: mainly depression, delusions, confusion insomnia, hallucinations.

- **GIT:** Anorexia, nausea, vomiting (due to stimulation of chemoreceptor trigger zone, CTZ).
- **Cardiac** arrhythmias & orthostatic hypotension
- Mydriasis (narrow angle glaucoma)

Contraindication: Psychotic patient - Glaucoma (due to mydriatic effect) - history of melanoma cause its **precursor** of melanin

Limitations

- **Dyskinesia** (involuntary movements occurs in 40 to 90% of patients) **due to fluctuating plasma levels of L -dopa.**
- can be reduced by lowering the dosage; **howeve**r, the symptoms of parkinsonism may then reappear.
- **Wearing-off effect** (no effect) (shorter "**on**" states).
- **On-off phenomenon** (**On** → improved mobility / **Off** →Akinesia or hypomobility).
- **Wearing off effect & on-off phenomena occur due: progression** of disease & **loss** of **striatal dopamine** nerve terminals.

Drugs that increase dopaminergic activities

	Dopamine receptor agonists		Inhibition of DA metabolism	
Drug			MAO-B inhibitors Selegiline	COMT inhibitors Entacapone & Tolcapone
Characteristics	• longer duration of action than L-dopa [**Less likely** to cause dyskinesia than levodopa] • **As monotherapy**: **less** effective than L - dopa. • **advanced stages:** used as an adjunct to levodopa, & may contribute to clinical improvement &↓ levodopa dosage needs.		• **selective irreversible** MAO-B inhibitor • MAO-B is an important **enzyme** for dopamine metabolism • Blockade of dopamine metabolism makes **more dopamine** available for stimulation of its receptors • Has **neuroprotective** effect • **antioxidant activity** against toxic **free radicals** produced during dopamine metabolism • Selegiline is metabolized to desmethylselegiline, Which is **antiapoptotic**	• Acts **peripherally** to inhibit COMT enzyme required for L-dopa degradation → **Diminishes** peripheral metabolism of L-dopa
	Ergot	Non-Ergot		
Pharmaco kinetics	Bromocriptine - pergolide • **D2** agonist • **Oral** • **t½ = (** 6-8 h **)**	Pramipexole • **D3** agonist • **Oral** • excreted unchanged in urine		
Uses	• Parkinson's disease • **Hyper**prolactinemia **(galactorrhea)** • **Infertility** in women.	• **Alone** as initial therapy • **Combination** with L-Dopa	• **Adjunctive** to levodopa / carbidopa in later-stage parkinsonism to: ○ ↓ levodopa dose ○ **Delay** dyskinesia and fluctuation that accompany long term use of levodopa	• **adjuvant** to L-dopa to: ○ ↓ fluctuations ○ Improve response ○ Prolonged the ON-Time
ADV	Nausea, vomiting, postural **hypo**tension, **Cardiac** arrhythmias, Confusion, hallucinations, delusions, Dyskinesias **(less prominent).** somnolence(Sleepiness), also unnatural drowsiness		• **high doses → inhibit MAO-A → (hypertensive crises).** • **insomnia** when taken later during the day	• L-Dopa side effects. • **Orange** discoloration of 'urine
Contra-indication	• Psychosis • Peripheral vascular disease (**ergots**) because ergots cause sever vasoconstriction • Recent **Myocardial infarction [MI]**		• **should not** be co-administered with **tricyclic antidepressants**, or **selective serotonin reuptake inhibitors** → may cause hyperpyrexia, agitation, delirium, coma	--

	Drugs that increase dopaminergic activities	
Drug	DA releaser [amantadine]	Anticholinergic Drugs Benztropine, Trihexphenidyl
Characteristics	• originally introduced as an antiviral. • Amantadine increases dopamine release. • acts as an antagonist at **muscarinic** and **NMDA** receptors (N-methyl-D-aspartate). • **Less** efficacious than L-dopa • Tolerance → fter 6-8 months • Its benefits last only for **short period** and only used for L-dopa resistance • **Amantadine** and the **anticholinergics** may exert additive effects on mental functioning.	• Central muscarinic antagonist. • Has modest anti- parkinsonian actions. • They improve tremor & rigidity but have little effect on bradykinesia. • Provide benefit in drug-induced parkinsonism (due to antipsychotics). • used during the early stages of the disease or as an **adjunct to levodopa** therapy
Pharmaco kinetics	• **oral** • **short** half life • excreted unchanged in the **urine**	--

Adverse effects	• Nausea, anxiety, insomnia, confusion, hallucinations (dopamine like side effects).
	• Dry mouth, urinary retention (anticholinergic effects).
	• Restlessness and hallucinations (NMDA antagonist).
		• Cycloplegia, mydriasis, dry mouth, urinary retention, constipation.
		• Confusion, delirium, and hallucinations may occur at higher doses
		
		• Contraindications
		  ○ Prostatic hypertrophy
		  ○ Glaucoma
		  ○ Intestinal obstruction

Summary

- In mild cases, selegiline, amantadine or anticholinergics can be used.
- Levodopa and carbidopa is the main treatment
- All other medications are adjuncts to levodopa therapy
- Other useful drugs include bromocriptine (dopamine agonist), selegiline (monoamine oxidase-B inhibitor), amantadine (enhances dopamine release) and benztropine (muscarinic receptor antagonist, that is used for parkinsonism caused by antipsychotic drugs.

MCQ's

1) Antiviral drug found to have anti-parkinson's disease properties ?

a) Levodopa
b) Reserpine
c) Amantadine
d) Haloperidol

2) Dopamine agonist ergot derivative ,stimulate D2 receptors?

a) Selegiline
b) Pergolide
c) Levodopa
d) Amantadine

3) an Anti-parkinson's drug , also used to treat hyperprolactinemia?

A)amantadine
B)benztropine
C)levodopa
D)Bromocriptine

4)selective MAO-B inhibitor ?

A)phenelzine
B)selegiline
C)paramipexole
D)moclobemide

5)a parkinsonism patient had a prescription of anti-parkinson's drug , after 2 weeks he noticed orange discoloration of his urine .What is the drug which was prescribed by his doctor ?

A) selegiline
B)benzotropine
C)Tolcapone

6)A parkinsonism patient is taking vitamin B6 ,which one of these drugs is contraindication to him ?

a)Levodopa
b)Benztropine
c)Amantadine

7)An antiemetic drug causes Parkinson disease?

a)Haloperidol
b)Metoclopramide
c)pyridoxine

1:c 2:b 3:d 4:b 5:c 6:a 7:b

Good luck!

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