MED437
KING SAUD UNIVERSITY

Pharmacology
435 team

Pharmacology
Team 437

Drugs used for Parkinsonism

Objectives:

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

Color index:

- Drugs names
- Doctors notes
- Important
- Extra

Editing File

To Understand better

Parkinson's Disease

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

Pathophysiology

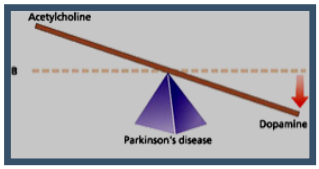
This **movement** disorder occurs mainly due to **dopamine/acetylcholine imbalance** in **basal ganglia** (caudate nucleus, substantia nigra & corpus striatum) that is involved in motor control.

Dopamine pathway

Reward pathway	Motor pathway
DA is manufactured in nerve cell bodies located within the ventral tegmental area (VTA) and is released in the **nucleus accumbens** and the **prefrontal cortex.**	cell bodies in the **substantia nigra** that manufacture and release dopamine into the **striatum**.

In Parkinson's disease

Predominance of Ach



Deficiency of dopamine

Parkinson's Disease

Character

Simplified by the acronym **-TRAP-**

- **T**remors at rest.
- **R**igidity of muscles.
- **A**kinesia or Bradykinesia
- (slowness in initiating and carrying out voluntary movements).
- **P**ostural and gait abnormalities.
- Anxiety or depression.

Causes

It is an **idiopathic** disease but some causes may be:

- Genetic.
- Toxins (MPTP= methyl phenyl tetrahydropyridine).
- Head trauma.
- Cerebral anoxia.
- Oxidative stress
- Drug-induced Parkinson's disease

e.g. **antipsychotics** like **haloperidol**. **Dopamine antagonists** as **metoclopramide** (antiemetic).

Drug Treatment

Main approach

Drugs to **increase dopaminergic** activity.

- **Increase** central DA synthesis
  - **(DA precursors):** L-dopa, L-dopa + Decarboxylase inhibitor.
- **Inhibition** of DA metabolism
  - **- COMT inhibitors** (catechol-O-methyltransferase inhibitors)
  - **-MAO-B inhibitors**
- DA receptor agonists
- DA releaser: **amantadine**

Minor approach

Drugs to **block cholinergic** activity → **Muscarinic antagonists e.g. benztropine, trihexyphenidyl**

Patients with Parkinson have deficiency of DA, to treat them we can't give only DA. Why? Dopamine is a polar can not cross the blood brain barrier →can not produce action.

Drugs used in parkinsonism

- **Mild cases** → **Selegiline**, **Amantadine** or **Anticholinergics**
- **Main treatment** → **Levodopa** + **Carbidopa**
- **Adjuncts to Levodopa** → All other medications
- **Other useful drugs**
  - Dopamine agonist → **Bromocriptine**
  - MAO-**B** inhibitors → **Selegiline**
  - Enhance dopamine release → **Amantadine**
  - Muscarinic receptor antagonist → **Benztropine** and **trihexyphenidyl**

It is a minor treatment, if he can not take dopamine → give him antimuscarinic drugs. Like in patient with psychotic disease

Drugs that increase dopaminergic activities (DA precursors)

Drug

Levodopa (L-dopa)

Pharmacokinetics

- It is a precursor of dopamine.L-dopa is a replacement therapy, it's not prevent the progression of the disease
- Is converted into dopamine via **dopa decarboxylase** (DC) peripherally and centrally. → Pathway of L-dopa
- Dopamine formed peripherally is metabolized by **MAO** (monoamine oxidase) & **COMT** (catechol-o-methyltransferase enzymes).
- 99% L-dopa is **decarboxylated** to give dopamine in gut and liver by **decarboxylase** enzyme to be only peripherally, make it polar enzyme .
- **1%** crosses **BBB** to form dopamine centrally.
- Given **orally** (should be taken on **empty** stomach (especially proteins-).
- Absorbed from the small intestine and taken up to CNS by **active** transport system. → So if we take a protein meal → uptake process done by competition process between the amino acids & L-dopa.
- **Short** duration of action (**t½ = 2 hs**) → (fluctuation of plasma concentration).

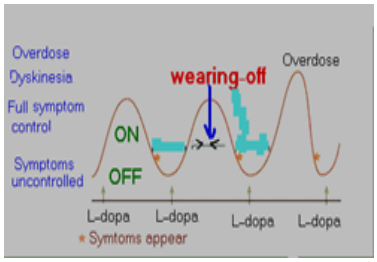
Limitation

Limitation of L-DOPA treatment:

- **Dyskinesia** (involuntary movements occurs in 40 to 90% of patients) → due to fluctuating plasma levels of **levodopa**. (يعني تركيزه غير ثابت، يزيد وينقص)
- The dyskinesia can be reduced by **lowering the dosage**; however, the symptoms of parkinsonism may then reappear.
- **Wearing-off effect** (duration of "on" states becomes shorter) → معناها إن الأون إفكت حق الإل دوبا بدأ يقل
- **On-off phenomenon** (On= improved mobility & Off=Akinesia or hypomobility) → bc of short $T_{1\backslash 2}$

On: الدواء في therapeutic range
Off: الدواء قل تركيزه في الدم فقلت فعاليته؛ فتأثر المريض بالحركة .فلما يكون جالس ونقول له قم ما راح يقدر يقوم، ويبدأ يتلعثم في الكلام؛ كل هذا عشان تركيز الدواء قل وبالتالي قلت فعاليته في التحكم بالحركة.

- Wearing off effect and on-off phenomena occur due to → **progression** of the disease and the **loss** of striatal dopamine nerve terminals.



في المستطيل الأخضر، يعني إن الدواء في ال therapeutic range ويصير عندنا ال **on** phenomenon

فوق المستطيل، بيصير تركيزه عالي في الدم، وتحت المستطيل يقل التركيز، ويصير عندنا ال **off** phenomenon

a body shamer say's: leave = ! اتركوا الدبا dopa
*Body shaming: the act of discriminating against other body types.

Drug	Levodopa (L-dopa) cont.
P.D	- Dopamine acts on dopaminergic receptors D1-D5 (**G-protein linked receptors**) - **D1**, **D5** → Excitatory. - **D2**, **D3**, **D4** → Inhibitory.
prescription	**L-dopa** is usually combined with **carbidopa** or **benserazide** (**DC inhibitor**). → Why? → because Carbidopa is a peripheral dopa decarboxylase inhibitor → prevent GIT & peripheral conversion of **L-dopa** to dopamine. → It acts only peripherally because it does **not** cross BBB → ↑ **T1\2** => Why only peripherally? Because when it acts also centrally, we won't take the benefit because L-dopa will not be degraded to produce dopamine. **- Benefit of L-dopa + carbidopa combination:** - **Lowers** the effective levodopa dose. - **Increase availability** of L-dopa to CNS. - **Reduce side effects** of L-dopa **take L Dopa on empty stomach because if eaten with food may interfere with amino acid**
Indications	- The most efficacious therapy. → 1st line treatment. - The 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. - Should **not** be used in parkinsonism associated with antipsychotic drug therapy.
Drug interaction	- High proteins meals. (compensate on the same receptors) - **Pyridoxine** (Vitamin B6). => ↓ effect of L-dopa due to ↑ peripheral metabolism by Vit.B6. - **Non Selective MAO inhibitors (phenelzine). => Hypertensive crisis** due to ↑ catecholamines => sever elevation of BP => Do not take MAOIs w\ any drug has catecholamine effects, because it will increase their level => hypersensitivity crisis. * tyramine has similar effect of MAO inhibitors.
ADRs	**Peripheral effects:** - Anorexia, nausea, **vomiting** (due to stimulation of chemoreceptor trigger zone). → They are more common w\ combination of DC inhibitors. - Cardiac arrhythmias. → because of increased catecholamines peripherally. **-Mydriasis** → May occur and participate in acute glaucoma. - **Orthostatic (postural) hypotension** → w\ higher doses. - **CNS effects:** Mainly **depression**, delusions, confusion, insomnia, **hallucinations**.
C.I	- Patients with history of **melanoma.** Why? → L-dopa is a precursor of **melanin** → so it may activate malignant melanoma. - **Psychotic patient**. → bc it may exacerbate the mental disturbance. - **Glaucoma** (due to mydriatic effect).

Dopamine receptor agonists

Overview

- **Have longer duration of action than L-dopa** (less likely to cause **dyskinesias** than **levodopa**)

Clinical use

- **As monotherapy,** the dopamine agonists are **less effective** than **levodopa**. This can only be used as initial therapy for **early** stages of the disease.
- **In advanced stages, dopamine agonists are used as an adjunct to levodopa,** they may contribute to clinical improvement and reduce **levodopa** dosage needs.
- Lippincott: Dopamine agonists may delay the need to use levodopa therapy in early Parkinson disease and may decrease the dose of levodopa in advanced Parkinson disease.

Ergot derivatives: Bromocriptine, pergolide	Non ergot derivatives
Bromocriptine	**Pramipexol**
• D2 agonist • Is given orally • T½ = 6-8 h. Longer than Levodopa (t½ =2 h) ButL-dopa more effective. • Used for the **treatment** of: 1. Parkinson's disease 2. Hyperprolactinemia (**galactorrhea**): a condition of elevated serum prolactin «هرمون الحليب», which induces infertility in women. Secretion of prolactin is under **inhibitory** control by dopamine. → كلما زاد البرولاكتين قل مستوى الدوبامين. **3. Infertility in women.**	• D3 agonist • Used alone as **initial therapy** or in combination with L-dopa. • Is given **orally**, excreted unchanged in urine. • Has the advantage of being **free radicals scavenger**.

Adverse effects

Similar to **L-dopa**:

- Nausea, vomiting, postural hypotension
- Cardiac arrhythmias
- **Confusion, hallucinations, delusions**
- Dyskinesias **(less prominent).**

Contraindications

- **Psychosis**
- Peripheral vascular disease (**only ergot derivatives**, which cause severe vaso**constriction** and may cause gangrene with high dosage)
- Recent **myocardial infarction** .

Amantadine

Characteristics

- originally introduced as an **antiviral**.
- Action:
  - **-Increases dopamine release**. → Also decrease the reuptake of DA.
  - -Acts as an **antagonist at muscarinic receptors**
  - **-Antagonist at NMDA** receptors (N-methyl-D-aspartate) (glutamate receptors)

Administration:

- given **orally** with short half life.

Excretion:

- most of the drug is excreted unchanged in the **urine**

Efficacy:

- Less efficacious than L-dopa
- **Tolerance** develops to its therapeutic effect after **6-8** months. (tolerance is after 3-5 years for levodopa)
- Its benefits last only for **short period** and only used for **L-dopa resistance** (which is caused by variation in response among patients)
- **Amantadine** and the anticholinergics may exert **additive effects on mental functioning**. (A muscarinic receptor antagonist effect)
- Useful in the **early stages** of parkinsonism or as an **adjunct to levodopa therapy**. only when L-dopa not working

Adverse effects

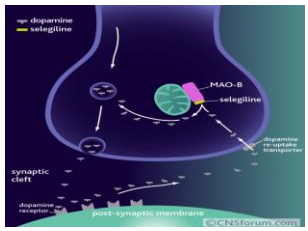
- Nausea, anxiety, insomnia, confusion, hallucinations (**dopamine** like side effects).
- Dry mouth, urinary retention (**anticholinergic** effects).
- Restlessness and **hallucinations** (**NMDA antagonist**). → NMDA is a type of glutamate receptors & glutamate is an excitatory neurotransmitter, antagonizing it will thus cause restlessness and hallucinations.
- **Ankle edema**, and **livedo reticularis**. →

COMT Inhibitors

(Catechol-O-methyltransferase) Inhibitors

Drug	Entacapone	Tolcapone
M.O.A	- Acts **peripherally** to inhibit COMT enzyme required for L-dopa degradation. - Usually given **in combination** with L-dopa and **carbidopa** to diminishes peripheral metabolism of L-dopa.	- **Peripheral** and **central** COMT inhibitor → More **lipid soluble** than **entacapone**. - More penetration into CNS. - **Tole** = Total = Central & peripheral
Indications	Used as adjuvant to **L-dopa + carbidopa** to: - Decrease fluctuations - Improve response - Prolonged the **ON-Time** → يحسن حالة المريض لأن الدوبامين جالس وقت أكثر	
ADRs	- **L-dopa** side effects. - **Orange** discoloration of urine.	---

Monoamine oxidase-B (MAO-B) inhibitors

Drug	Selegiline
M.O.A	- It is a **selective irreversible inhibitor of MAO-B**, an important enzyme for **dopamine metabolism**. * MAO-A → metabolize **NE**, **5-HT**, **DA** - The blockade of dopamine metabolism makes **more** dopamine available for stimulation of its receptors. 
P.K	• **Selegiline** may have **neuroprotective effect** due to: **- Antioxidant activity** against toxic free radicals produced during dopamine metabolism. - Metabolized to **desmethyl selegiline**, which is **anti-apoptotic**.
Indications	Adjunctive to levodopa/carbidopa in **later-stage** parkinsonism to: - Reduce the required dose of **levodopa** - Delay the onset of **dyskinesia** and motor fluctuations that usually accompany long-term treatment with **levodopa**.
ADRs	At high doses: - It may **inhibit MAO-A** → (**hypertensive crises**) → as a result, do not prescribe selegiline w\ drugs that increase the level of catecholamines and lead to hypertensive - May cause **insomnia** when taking later during the day.
C.I	Should NOT be co-administered with: - **Tricyclic** Antidepressants - Selective serotonin reuptake inhibitors (this causes **hyperpyrexia**, agitation, delirium, coma.) → Serotonin toxicity. - Food restriction "**low tyramine diet**" is required. → increase release of E & NE → sever elevation in BP (**cheese effect**)

Anticholinergic Drugs

Drug	Benztropine	Trihexyphenidyl
M.O.A	- **Central muscarinic antagonist**. - It has **modest** anti-parkinsonian action.	
Indications	- **Improve tremor & rigidity**. (but have little effect on **bradykinesia**. - Provide benefit in **drug-induced parkinsonism** (due to **antipsychotics**). - Used during **early** stage of the disease - Used as an **adjunct** to **levodopa** therapy.	
ADRs	- Cycloplegia - Mydriasis - Dry mouth - Urinary retention - **Constipation** - **At high doses**: Confusion, Delirium & Hallucinations.	
C.I	- Prostatic hypertrophy - Glaucoma - **Intestinal obstruction**.	

Questions

MCQs

1. **What is the most efficacious Drug in treatment of Parkinson's?**

A) Selegiline
B) Benztropine
C) Levodopa
D) Pramipexole

2. **A patient with glaucoma developed Parkinson's, which Drug should not be prescribed?**

A) Levodopa
B) Entacapone
C) Pergolide
D) Pramipexole

3. **Which of the following can be prescribed with the drug of choice to decrease dyskinesia?**

A) Benztropine
B) Trihexyphenidyl
C) Tolcapone
D) Bromocriptine

4. **A patient with advanced Parkinson's needs an adjuvant drug added to her treatment. She has Raynaud's disease. Which of the following should be prescribed?**

A) Pramipexole
B) Bromocriptine
C) Pergolide
D) Amantadine

C A D D

Questions

MCQs

5. A patient with advanced Parkinson's was prescribed an adjunct to his therapy. He later developed livedo reticularis. Which of the following was he prescribed?

A) Pergolide
B) Amantadine
C) Pramipexole
D) Bromocriptine

6. Which of the following is a Peripheral side effect to L-dopa?

A) Anorexia
B) Delusions
C) Insomnia
D) Erectile dysfunction

7. Which of the following can cause hypertensive crisis in high doses?

A) Amantadine
B) Bromocriptine
C) Selegiline
D) Pergolide

8. Which of the following can be used with antipsychotics?

A) Levodopa
B) Carbidopa
C) Entacapone
D) Benztropine

D
C
A
B

Questions

SAQ

What features of Selegiline give it a neuroprotective effect?

- Antioxidant activity against toxic free radicals produced during dopamine metabolism.
- Selegiline is metabolized to desmethylselegiline, which is antiapoptotic.

Describe the action of L-dopa:

It is a precursor of dopamine (converted into dopamine peripherally and centrally) by the action of an enzyme called dopa decarboxylase (DC). 99% is metabolized peripherally by MAO and COMT and only 1% crosses the BBB.

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References:

- Doctors' slides and notes.
- pharmacology Team 435.

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