pharmacology
Team 438

MED438
KING SAUD UNIVERSITY

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Neuropsychiatry Block

Pharmacology Team 438

Drugs Used in Parkinsonism

Objectives

By the end of the lecture , you should know:

- 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:

Black : Main content
Red : Important
Blue: Males' slides only
Pink : Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Editing File

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.

Reward 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**

Dopamine pathway

Motor pathway

cell bodies in the **substantia nigra** that manufacture and release dopamine into the striatum.

- Note then in parkinson's disease there is Predominance of **Ach** & Deficiency of **dopamine**

Causes & Characters of the Disease

Characters

Simplified by the acronym -TRAP-
- Tremors at rest.
- Rigidity of muscles
- Akinesia or Bradykinesia
(slowness in initiating and carrying out voluntary movements).
- Postural and gait abnormalities.
- Anxiety or depression.

Causes

It is idiopathic disease but some causes may be:
- Genetic.
- Toxins (MPTP= methyl phenyl tetrahydropyridine).[1]
- Head trauma.
- Cerebral anoxia.
- Oxidative stress
- Drug-induced Parkinson's disease e.g.
1-antipsychotics as **haloperidol.**
2- Dopamine antagonists as **metoclopramide** (antiemetic)

Drugs Used for the Treatment [2]

Major Approach:
Drugs to increase dopaminergic activity

- **Dopamine precursor:**[3] L-dopa+Carbidopa
- **Dopamine releaser:** Amantadine
- Dopamine Agonist:
a) Ergot: Bromocriptine & Pergolide
b) Non-ergot: Pramipexole
- **COMT inhibitors:** Entacapone
- **MAO-B inhibitors:** Selegiline

Minor Approach:
Drugs to block cholinergic activity

- **Muscarinic Antagonist:** Benztropine & Trihexyphenidyl

1- it is a substance used on experimental animals that induces parkinson-like symptoms to test drugs for parkinson's
2-Dopaminergic neurons cannot be regenerated. We can only try to maintain the quality of life for parkinson's patients by increasing dopamine.
3- Patients with Parkinson have deficiency of DA, to treat them we can't give only DA. Why? Dopamine is a polar thus it can not cross the blood brain barrier →can not produce action.

DA precursore

Drug	Levodopa (L-Dopa) **First line**
Over-View	• It is a precursor of dopamine. • Is converted into dopamine via **dopa decarboxylase** (DC) **peripherally and centrally**. • 99% L-dopa is decarboxylated to give dopamine in gut and liver.[1] • Dopamine formed peripherally is metabolized by **MAO** (monoamine oxidase) & **COMT** (catechol-o-methyltransferase enzymes). • **1%** crosses **BBB** to form dopamine centrally. ★ L-dopa is usually given combined with **DC inhibitors (carbidopa or benserazide)** (dose reduction to 1/8) to prevent peripheral conversion of L-dopa to dopamine.
DC inhibitors	• E.g **Carbidopa** , Benserazide • They inhibit peripheral conversion of L-dopa to dopamine in GIT and other peripheral tissues. Thus, increasing T1\2. Why do DC inhibitors act only Peripherally? it's water-soluble & unable to cross BBB, and that's an advantage because it won't work in the CNS. thus L-dopa is converted to dopamine only in the CNS. ★ **Benefits of L-dopa+carbidopa combination:** ○ Lowers the effective levodopa dose ○ Increase availability of levodopa to CNS. ○ Reduce dose of levodopa and side effects.
P.K	• Given orally **(should be taken on empty stomach).** • absorbed from the small intestine and taken up to CNS by active transport system. • High protein meal interferes with its absorption and transport into CNS • Short duration of action (t1⁄2 =2 h)(fluctuation of plasma concentration).
MOA	• Dopamine acts on dopaminergic receptors D1-D5 (**G-protein linked receptors**) ○ **D1, D5** → Excitatory ○ **D2, D3, D4** → Inhibitory
Uses	★ Effective against all types of parkinsonism in the first few years (particularly bradykinesia & rigidity) **except** those associated with antipsychotic drug therapy. • does not cure the disease.
ADRs	**CNS effects (Psychological disorders):** • Mainly depression • Vivid dreams • Delusions • Hallucinations • Confusion • Sleep disturbances (insomnia). **Peripheral effects:** • Anorexia, nausea, vomiting (due to stimulation of CTZ). • Cardiac arrhythmias (withdraw the drug). • Mydriasis • Orthostatic hypotension.
Limitation	• **Dyskinesia** (involuntary movements occurs in 40 to 90% of patients) → due to **fluctuating plasma levels of levodopa**. • 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) [2] • **On-off phenomenon**[3] (On= improved mobility & Off=Akinesia or hypomobility) • Wearing off effect and on-off phenomena occur due to **progression of the disease and the loss of striatal dopamine nerve terminals.**

1- which renders the L-dopa insufficient alone and it must be taken with another drug(DC inhibitors) to prevent the peripheral conversion of L-dopa to dopamine. So that it will only turn into dopamine centrally or after crossing the BBB.
2- usually occurs within 3-5 years of starting L-dopa. And it's prevented by increasing the frequency, or adding other dopamine agonist drugs, or sustained release.
3- due to chronic use, and it's solved by depriving the patient from L-dopa then giving it back again.

Drug	Levodopa (L-Dopa) cont...
Drug Inter-actions	• High protein meal[1] • Pyridoxine (Vitamin B6)[2] • Non Selective MAO inhibitors (Phenelzine, Tranylcypromine)→ Hypertensive crisis
C.I	• Psychotic patient • Glaucoma (due to mydriatic effect) • Patients with history of melanoma ○ **Why?** L-dopa is a precursor of melanin • Cardiac arrhythmias or recent cardial infarction. • Adrenomimetic amines

Dopamine receptor agonist

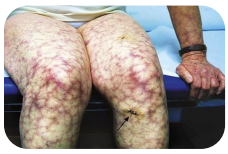
Ergot Derivatives:
Bromocriptine , Pergolide

synthetics(Non-Ergot Derivatives):
Pramipexole, Ropinirole

Over-View	• Have longer duration of action than L-dopa (less likely to cause **dyskinesias** than levodopa)[3]
Clinical use	• **As monotherapy**, the dopamine agonists are **less effective** than levodopa. • **In advanced stages,** dopamine agonists are used as an **adjunct** to levodopa, they may contribute to **clinical improvement** and reduce levodopa dosage needs.

Drug	Bromocriptine	Pramipexole
P.K	• D2 agonist and partial D1 antagonist • Is given orally, absorbed from GIT • T½ = 6-8 h. • Excreted in bile and feces	• D3 agonist • Is given orally • Has the advantage of being free radicals scavenger. AKA anti-oxidant. • Rapidly absorbed, excreted unchanged in urine • Renal insufficiency may necessitate dosage adjustment
Uses	• Parkinson's disease (Little use) • Hyperprolactinemia **(galactorrhea)** • **Infertility in women.** [4]	• Used alone as **initial therapy** or in combination with L- dopa.
ADRs	Similar to L-dopa: • Nausea, vomiting, somnolence, postural hypotension • Cardiac arrhythmias • Confusion, hallucinations, delusions • Dyskinesias **(less prominent)**	
C.I	• Psychosis • Peripheral vascular disease (**only ergot derivatives**). e.g Raynaud's disease (which causes severe vaso**constriction** and may cause gangrene with high dosage) • Recent myocardial infarction • Active peptic ulcer	

1- competition occurs on the same receptors.
2- vitamin B6 functions as a cofactor for DC, thus taking L-dopa+Pyridoxine-> will result in more peripheral conversion of L-dopa to DA and decreases the utilization of DA centrally. However, taking L-dopa + Carbidopa + Pyridoxine is actually recommended. (because the peripheral conversion is now inhibited while the central is functional and will increase the levels of DA in the CNS)
3- less likely to fluctuate.
4- due to the increase in prolactin levels.

Drug	Amantadine
MOA	• Modest effectiveness • originally introduced as an **antiviral.** ★ **Inhibits dopamine reuptake, thus increases dopamine release** • Acts as an **antagonist at muscarinic & NMDA** receptors (N-methyl-D-aspartate)
P.K	• given **orally** with short half life 2-4h. • most of the drug is excreted unchanged in the **urine** • Less efficacious than L-dopa • **Tolerance** develops to its therapeutic effect after **6-8** months.
Uses	• Its benefits last only for **short period** and only used for **L-dopa resistance.** ★ Useful in the **early stages** of parkinsonism or as an **adjunct to levodopa therapy** • Amantadine and the anticholinergics may exert additive effects on mental functioning.
ADRs	• Nausea, anxiety, insomnia, confusion, hallucinations (**dopamine** like side effects). • Dry mouth, urinary retention (**anticholinergic** effects). • Restlessness and **hallucinations** • **Ankle edema**, and **livedo reticularis** [1] 
C.I	• Anticholinergics • History of seizures or heart failure

MAO-B inhibitors

Drug	Selegiline
MOA	• It is a **selective irreversible inhibitor of MAO-B**, an important enzyme for **dopamine metabolism**. • 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, so It slows progression of the disease. • Metabolized to **desmethyl selegiline**, which is **anti-apoptotic**.
Uses	• As monotherapy, may be effective in the newly diagnosed patient 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**) • May cause **insomnia** when taking later during the day. • May Increase L-dopa ADRS
C.I	co-administered with: • Tricyclic Antidepressants (hypertensive crisis), meperidine • Selective serotonin reuptake inhibitors (may cause hyperpyrexia, agitation, delirium, coma.) (Serotonin syndrome) ★ Food restriction **"low tyramine diet"** is required [2]

1- Formation of small blood clots all over the body, it's one of the few drugs that cause this.
2- To avoid the hypertensive crisis, because tyramine increases the release of NE & E.
Tyramine is found in the fermented food such as cheese, sausage, salami, & wine.

COMT Inhibitors Inhibitors Girls slides

Drug	Entacapone	Tolcapone
MOA	• 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.
Uses	Used as adjuvant to **L-dopa + carbidopa** to: • Decrease fluctuations • Improve response ★ Prolonged the **ON-Time**	
ADRs	• L-dopa side effects ★ Orange discoloration of urine	-

Anticholinergic Drugs

Drug	Benztropine	Trihexyphenidyl
MOA	• **Central muscarinic antagonist,** In the striatum. • It has **modest** anti-parkinsonian action	
Uses	• **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 or **adjunct** to levodopa therapy.	
ADRs	• Cycloplegia • Mydriasis • Dry mouth • Urinary retention • Constipation • **At high doses**: Confusion,Delirium & Hallucinations • Trihexyphenidyl may cause withdrawal symptoms in high doses.	
C.I	• Prostatic hypertrophy • Glaucoma • Intestinal obstruction.	

Summary from Dr. slides

main treatment:
Levodopa and carbidopa

Mild cases:
- selegiline
- amantadine
- anticholinergics

All other medications are adjuncts to levodopa therapy

Doctors case

M. S. is a 60-year old architect who designs buildings. His drawings are very detailed and they must be drawn to a specific scale. During the past month he has developed a slight tremor in his right hand that causes some embarrassment but does not interfere with function. He has, however, noticed that his writing and drawing have gotten much smaller, causing problems with his work. His primary care physician has referred him to a neurologist for evaluation. On examination, the neurologist notes some motor rigidity in the right arm. He also observes a slight slowing in the patient's walk and a reduction in the swing of his arms as he walks. What is the diagnosis, and how should the patient be treated?

Ans:
The patient is in early-stage parkinsonism, most likely idiopathic (Parkinson's disease).
Clinically, the disease is very mild and the neurologist might consider not treating him at this point, but because the micrographia interferes with his work, the neurologist decides to prescribe medication.
Several drugs can be used to treat early-onset parkinsonism, the most commonly used are the dopamine receptor agonists (pramipexole, ropinirole, pergolide) amantadine is also a possibility, and some people get an acceptable response to selegiline (the MAO inhibitor).
Levodopa–carbidopa could also be used; however, most clinicians prefer to delay its use until absolutely needed because of the adverse effects, such as motor fluctuations and dyskinesias, that accompany long-term use of levodopa.

Great caution must be exercised in the use of this drug in parkinsonian patients who have prostatic hypertrophy :-

(A) Benztropine

(B) Carbidopa

(C) Levodopa

(D) Bromocriptine

(E) Selegiline

Ans : A

A drug that is used in the treatment of parkinsonism and will also attenuate reversible extrapyramidal side effects of neuroleptics is :-

(A) Amantadine

(B) Levodopa

(C) Pergolide

(D) Selegiline

(E) Trihexyphenidyl

Ans: A,E

Quiz

MCQ

Q1- A 63-year-old man with debilitating Parkinson's disease is currently taking levodopa. His primary care physician adds carbidopa to his treatment regimen. One week later, the patient presents to the emergency department complaining of anorexia, nausea, and vomiting. What is the most likely explanation for these findings?

(A) Drug toxicity
(B) Idiosyncratic drug reaction
(C) Stimulation of the chemoreceptor trigger zone
(D) Underlying infection

Q2- A 72-year-old woman with Parkinson's disease is taking a medication that increases release of dopamine, blockade of cholinergic receptors, and inhibiting the N-methyl-d-aspartate receptor. This describes which of the following agents?

(A) Amantadine
(B) Bromocriptine
(C) Pramipexole
(D) Rotigotine

Q3- Which one of the following is the effect of Pyridoxine on L-dopa?

(A) Enhance L- dopa effect
(B)Diminish L- dopa effect
(C) no effect
(D)increase its Potency

Q4- A 58-year-old man with Parkinson's disease presents to the clinic for follow-up. Recently, he has experienced an increase in his resting tremor and rigidity. He was wondering if there is a medication that could help these symptoms. What anticholinergic is the most appropriate treatment?

(A) Benztropine
(B) Bromocriptine
(C) Ipratropium
(D) Scopolamine

Q5- What is the ADR of Bromocriptine?

(A) Ankle edema
(B)orange discoloration of urine
(C) peripheral vascular disease
(D)Hypertension crisis

Answers:

MCQ

Q1	C	Q2	A	Q3	B	Q4	A	Q5	C

pharmacology

Team 438

Good Luck , Future Doctors!

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Share with us your ideas !