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RESEARCH ARTICLE
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REVIEW ON ANTI-PARKINSONS DRUGS

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Abstract
This review the discussion was about the prevalence, awareness, diagnosis, treatment, and control of Parkinson's disease in older adults. Parkinson's Disease is the second most common progressive neurodegenerative disorder affecting older adults Resulting from a pathophysiologic loss or degeneration of dopaminergic neurons in the substantia nigra of the midbrain and the development of neuronal Lewy Bodies, idiopathic Parkinson's Disease is associated with risk factors including aging, family history, pesticide exposure and environmental chemicals (e.g., synthetic heroin use). Its ultimate cause(s) is (are) unknown.Characterized by both motor and non-motor symptoms, PD patients classically display rest tremor, Muscular rigidity, Loss of associated movements, hypokinesia, etc.

Keywords: Parkinson’s disease, treatment, motor and non-motor symptoms, Anti-Parkinson’s drugs, etc.

INTRODUCTION

Parkinsonism is slowly progressive degenerative disease. It is a syndrome of varied etiology. Important featuresobserved are:

- Akinesia: It associates with loss or impairment of the power of voluntary movement.
- Muscular rigidity.
- Postural in stability: It is due to the hypokinesia i.e. partial or complete loss of muscle movement.
- Tremor.

- Loss of associated movements.

Pathophysiology:

Degeneration of the dopamine- producing neurons in the substantia nigra of the midbrain

↓

Disrupts the normal balance between Dopamine (DA) and acetylcholine (Ach) in the basal ganglia.

↓

Impaired extra pyramidal tract controlling

↓

Loss of motor control

↓

Tremor, rigidity and Akinesia.

Basal ganglia control and regulate the activities of motor and pre motor cortical areas so that voluntary movement can be performed smoothly. The basal ganglia consist of the corpus striatum, Globuspallidus and Substantianigra.

Substantianigra is rich in dopaminergic neuronal cell bodies, which is projected to the corpus striatum where dopamine is released. Also protect back via Globuspallidus to thalamus and cerebral (i.e. motor cortex) and regulates their involvement in voluntary movements.

The nigro-striated neurons make efferent connection with striatum where they make contact with two types of neurons, bearing two receptors i.e. D1 and D2 receptor. The nigro neurons which bear Di receptor relay impulses via direct pathway. The pathway begins through medial Globuspallidus-thalamus-cerebralmotorcortexto enhancestimulation of spinal motorneurons. On the other hand the neurons which bear D; receptor relay impulses via an indirect pathway i.e. through lateral Globuspallidus- sub thalamic nucleus - Medial globus pallidus thalamus same cerebral motor cortical neuron decreases stimulation of spinal motor neurons.

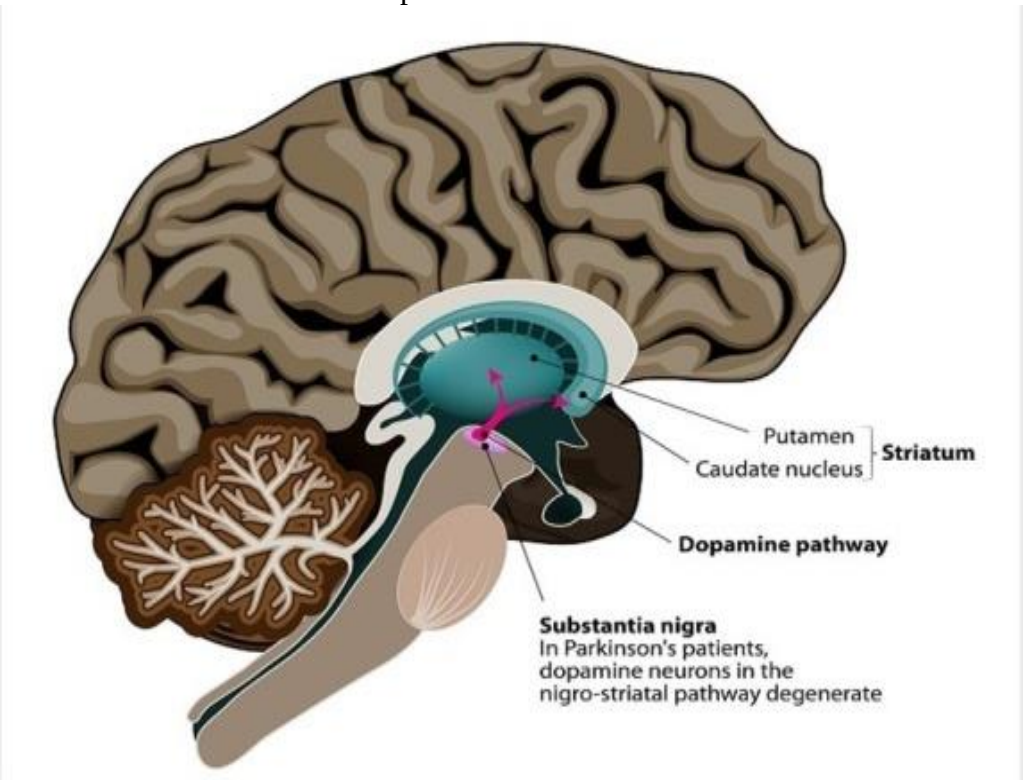

Fig. location of Parkinson's disease in brain

In PD, dopamine deficiency, which occurs as a result of degeneration of nigrostriatal dopaminergic neurons, leads to dominance of indirect pathway. Whereas in healthy predominance of direct pathway Le. Released of dopamine in corpus striatum enhance the activity of neurons.

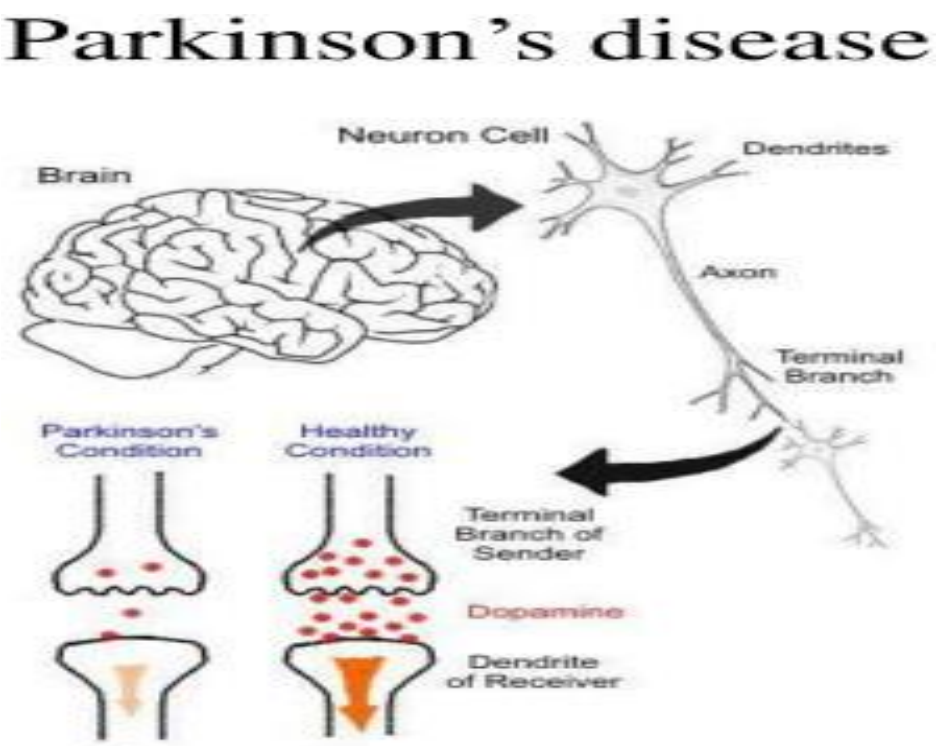

Fig. Effect of dopamine in normal condition and PD condition.

Major pathology is the Degeneration of Dopaminergic neuron in-substanianigra nigrostriatal tract of basal ganglia.
Imbalance occurs between Dopaminergic (Inhibitors) and Cholinergic (facilitarory System) Parkinsonism.

Factors Contributing Degeneration of Dopaminergic Neurons:

- Aging
- Genetic predisposition
- Defective energy metabolism.
- ToxinslikeMPTF(N-methyl-4-phenyl-tetrahydropyridine)
- Oxidation of dopamine by MAO-Band aldehydede hydrogenase.
- Normally: -There is Balance between Dopamine and ACH in striatum.
- Parkinsonism: Deficiency of Dopamine Lead to relatively increased ACH in Brain.
- Balance between Dopamine and ACH is restored with use of Anti Parkinsonism.

Symptoms:

Motor symptoms:

- Tremor
- Slow movement
- Stiffness
- Reduced facial expressions
- Change in posture walking or balance problems

Non-motor symptoms:

- Loss of sense of smell.

- Sleep problems Constipation Depression
- Daytime sleepiness
- Hallucinations
- Drop in blood pressure
- Psychosis.

CLASSIFICATION OF ANTIPARKINSONIAN DRUGS:

1. Drugs affecting brain dopaminergic system.

i. Dopamine precursor

a) Levodopa

ii. Dopaminergic agonists

a) Bromocriptine,
b) Ropinirole,
c) Pramipexole.

iii. MAO-B inhibitors

a) Selegiline,
b) Rasagiline.

iv. COMT inhibitors

a) Entacapone,
b) Tolcapone.

v. Glutamate (NMDA receptor) agonist

a) Amantadine.

vi. Peripheral decarboxylase inhibitors

a) Carbidopa,
b) Benserazide.

2. Drugs affecting brain cholinergic system

i. Central anticholinergic

a) Trihexyphenidyl,
b) Procyclidine,
c) Biperiden.

ii. Antihistaminic.

a) Ex.Orphenadrine,
b) Promethazine.

1] Drugs affecting brain dopaminergic system.

i]. Dopamine precursor:

a]LEODOPA:

Levodopa is the first-line treatment for PD and is combined with a peripherally acting dopade carboxylase inhibitor such as carbidopa or benserazide, which reduces the dose needed by about 10-fold and diminishes the peripheral side effects. It is well absorbed from the small intestine a process that relies on active transport, although mucho fitis inactivated by MAO in the wall of the intestine.

Pharmacokinetics:

Orally the drug is absorbed in small intestine very rapidly. They follow the pattern of active transport mechanism. They show the first pass metabolism effect in liver. 95% of oral administration of leodopa rapidly converts into dopamine in presence decarboxyl as in the lumen and other tissues.

As we know that dopamine is poor to penetrate the blood brain barriers, therefore only1-3% of L-dopa which not converted to dopamine is available to penetrate blood brain barriers. So the large doses L-dopa are required to maintain the level of dopamine in the CNS. But the large doses of L-dopa may increase the unwanted effects

So as to maintain the blood level of L-dopa in the peripheral they are administered along with carbidopa or benserazide which are the decarboxylase inhibitors and prevents the peripheral synthesis of dopamine. The increased concentration of L-dopa in the peripheral will now readily penetrates the blood brain barriers.OnceL-dopa penetrates the BBB, further they will convert to dopamine because decarboxylase inhibitors are unable to penetrate the BBB. The dopamine will exert its activity. The carbidopa or benserazide reduces the dose of L-dopa by 10 folds and simultaneously decreases the peripheral side effects of L-dopa.

The plasma peak level reaches within ½ hour to 2 hours. The t1/2 of L-dopa is 1-2 hours. The bioavailability is 30% and excreted from renal about 70-80-%

The higher protein diet meal interferes the absorption of L- dopa because it is amino acid. Hence they are advised to take 1 hour before or after meal.

Levodopa is rapidly absorbed from the small intestines by utilizing the active transport process meant for aromatic amino acids. Bioavailability of levodopa is affected by:

(i) Gastric emptying: if slow, levodopa is exposed to degrading enzymes present in gut wall and liver for a longer time-less is available to penetrate blood-brain barrier.

(ii) Amino acids present in food compete for 1 the same carrier for absorption: blood levels are lower when taken with meals.

Levodopa undergoes high first pass metabolism in i.g .mucosa and liver. The peripheral and central pathway of metabolism of levodopa is depicted in about1% of administered levodopa that enters brain, aided by amino acid carrier mediated

High first pass metabolism in GI

The plasma T1/2 of levodopa (1, 2hrs.)

Bio-availability of levodopa affected by gastric emptying.

If slow levodopa to degrading enzyme present is gut wall and liver for a longer time.

Amino acid: present in food compete for same carrier for absorption.

Blood level: are lower when taken with meal.

ADVERSE EFFECTS:

The common adverse effects of Levodopa treatment are nausea, dizziness, headache, and somnolence. Special precaution is necessary for elderly patients because they may be more sensitive to the central nervous system (CNS) effects. The most common side effects in older patients taking levodopa can be confusion, hallucinations, delusions, psychosis, and agitation. There may be a greater risk of hip fractures in older adults due to levodopa mildly increasing homocysteine levels as an adverse effect. Abrupt withdrawal or dose reduction of levodopa is associated with an increased risk of neuroleptic malignant syndrome (NMS). This condition has been termed Parkinsonism hyperpyrexia syndrome. Hyperthermia, involuntary movements, and muscle rigidity are seen in severe cases. Management includes replacing levodopa at the prior doses and aggressive supportive care in an intensive care unit.

ii].Dopaminergic Agonists:

Dopamine agonists. These drugs act like dopamine in the brain. They include pramipexole (Mirapex), rotigotine (Neupro), and ropinirole (Reequip). Dopamine agonists don’t have the same risks of long-term problems as levodopa therapy. So they are often the first choice of treatment for Parkinson's disease.

a]. Bromocriptine:

It is anergot derivative which acts as potent agonist onD2receptors, but as partial agonist or antagonist on D1 receptors. Improvement in Parkinsonian symptoms occurs within 1hr of an oral dose of bromocriptine and lasts for 6-10hours. If use dalone, doses needed in Parkinsonism are high, and often produce intolerable side effects, especially vomiting, hallucinations, hypotension, nasal stuffiness, conjunctival injection. Marked fall in BP with the "first dose' has occurred in some patients, especially those on antihypertensive medication.

PROCTINAL, SICRIPTIN, PARLODEL, 1.25, 2.5mg tabs. ENCRIPT-2.5,5mg tabs.

b].Ropinirole and Pramipexole:

These are two nonergoline, selective D2/D3 receptor agonists with negligible affinity for DI and non dopaminergic receptors; Pramipexole has relatively greater affinity for D3 receptors. The therapeutic effect in PD as well as side effect profile is similar to bromocriptine, but they are better tolerated with fewer Symptoms. Ropinirole and pramipexole are now frequently used for monotherapy in early PD as well as to supplement levodopa-carbidopa in advanced cases. Trial shave found them to afford symptom relief nearly comparable to levodopa.

iii].MAO-B Inhibitor:

a]. Selegiline:

It is a selective and irreversible MAO-B inhibitor. Two is o enzyme forms of MAO, termed MAO-A and MAO-B are recognized; both are present in peripheral adrenergic structures and intestinal mucosa, while the latter predominates in the brain and blood platelets.

MAO-B preferentially oxidizes DA.Unlike non selective MAO inhibitors, selegiline in low doses (10 mg/day) does not interfere with peripheral metabolism of dietary amines; Accumulation of CAs and hypertensive reaction does not develop, while intracerebral degradation of DA is retarded. This is responsible for the therapeutic effect in Parkinsonism.

Difference in the course of the disease has been detected on follow up of selegiline treated patients in large multicentre studies. Never the less, there is some recent data support in ganeuro protective effect of rasagiline, another MAO-B inhibitor, in Parkinsonism.

Adverse Effects:

Postural hypotension, nausea, confusion, accentuation of levodopa induced involuntary movements and psychosis.

b]. Rasagiline:

Another newer selective MAO-B inhibitor with selegiline–like therapeutic effect in Parkinsonism. However, it is 5times more potent, longer acting and not metabolized to amphetamine.

iv].COMT INHIBITORS:

Two selective, potent and reversible COMT inhibitors Entacapone and Tolcapone have been introduced as adjuvant to levodopa-carbidopa for advanced PD. When peripheral decarboxylation of levodopa is blocked by carbidopa/benserazide, it is mainly metabolized by COMT to 3-O-methyldopa. Blocked of this pathway by entacapone/ tolcapone prolongs the t½ of levodopa and allows a larger fraction of administered dose to cross to brain. Vomiting, dyskinesia, postural hypo-tension, hallucinations, etc. occurs of ten when a COMT inhibitor is added. However, this can be minimized by adjustment of levodopa dose, which should be reduced by 20-30%. Other prominent side effect is diarrhea in 10-18% patients (less with entacapone) and yellow- orange discoloration of urine

v].GLUTAMATE (NMDA RECEPTOR) ANTAGONIST (Dopamine Facilitator):

More recently block of NMDA receptors subleasing closed states of the channel has been described and may be a novel target for anti-Parkinsonian drugs Amantadine is less effective than levodopa or bromocriptine in treating PD, but it is effective in reducing the dyskinesia induced by prolonged Amantadine can be used in milder cases, or in short courses to supplement levodopa for advanced cases. In the latter situation, it serves to suppress motor fluctuations and abnormal movements

Side Effects:

These are insomnia, restlessness, confusion, nightmares, anticholinergic effects and rarelyhallucinations.

Vi] Peripheral Decarboxylase Inhibitors:
Carbidopa and benserazide are extra cerebral dopade carboxylase inhibitors; they do not penetrate blood-brain barrier and do not inhibit conversion of levodopa to DA in the brain.
Benefits of the combination are-
1. The plasma t½ of levodopa is prolonged and its dose is reduced to approximately 1/4th.
2. Systemic concentration of DA is reduced, nausea and vomiting are minimized- therapeutic doses of levodopa can be attained more quickly.
3. Cardiac complications are reduced.
4. Pyridoxine reversal of levodopa effect does not occur.
5. "On-off effect is minimized since cerebral DA levels are more sustained.

2] Drugs affecting brain cholinergic system
i]. Central anticholinergic:
The central anti cholinergic act by reducing the unbalanced cholinergic activity in the striatum of Parkinsonian patients. These drugs produce 10-25% improvement in Parkinsonian symptoms lasting 4-8 hours after a single dose. Generally, tremor is benefited more than rigidity; hypokinesia is improved the least.
1. Tri-hexy-phenidyl (benzhesol):2-10mg/day; Pacitane, Parbenz 2mg tab.
2. Procyclidine:5-20mg/day:Kemadrin-25,5mg tab
3. Biperiden:2-10mgdayoral,im.oriv.:DYSKINON2mgtab.5mg/ml inj
4. Orphenadrine:100-300mg/day: DISIPALORPHIPAL50 mg tab,
5. Promethazine: 25-75mg/day :PHENERGAN10-25mg tab

Surgical Ways to Treat Parkinson's Include:
1]. Deep brain stimulation
2].Focused ultrasound
3]. Pallidotomy
4].Thalamotomy

Supportive therapies:
1]. Physiotherapy:
A physiotherapist can work with you to relieve muscles stiffness and joint pain through movement (manipulation) and exercise. The physiotherapist aims to make moving easier and improve your walking and flexibility.
- Massage
- Tai chi
- Yoga
- Meditation.

2]. Occupational therapy:
An occupational therapist can identify areas of difficulty in your everyday life, such as dressing yourself or getting to the local shops. They can help you work out practical solutions and ensure your home is safe and properly setup for you.

3].Speech and language therapy:
Many people with Parkinson's disease have swallowing difficulties (dysphasia) and problems with their speech. A speech and language therapist can often help you improve these problems by teaching speaking and swallowing exercises, or by providing assistive technology.

4]. Diet advice:
For some people with Parkinson's disease, making dietary changes can help improve some symptoms. These changes can include:

- Increasing the amount of fiber in your diet and making sure you're drinking enough fluid to reduce constipation
- Increasing the amount of salt in your diet and eating small, frequent meals to avoid problems with low blood pressure, such as dizziness when you stand up quickly
- Making changes to your diet to avoid unintentional weight loss

Discussion:

The most consistent lesion in PD is degeneration of neurones in the substantianigra pars compacta (SN-PC) and the nigrostriatal (dopaminergic) tract. This results in deficiency of dopamine (DA) in the striatum which controls muscle tone and coordinates movements. An imbalance between dopaminergic (inhibitory) and cholinergic (excitatory) system in the striatum occurs giving rise to the motor defect. Though the cholinergic system is not primarily affected, its suppression (by anticholinergics) tends to restore balance (DA↓, CA↑).

Conclusion:

- Parkinson's disease requires long term treatment
- Treatment of PD becomes challenging as time progresses
- In addition to medicines, remaining active, happy and doing regular exercise and physiotherapy are important
- There are some very good treatment options available and new drugs are being developed.
- In addition operations and drug delivery through routes other than mouth are becoming known and effective.

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