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Review Article

MEDICATION FOR PARKINSON's DISEASE: A REVIEW

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ABSTRACT

Parkinson's Disease is a complex neurodegenerative disorder in human. This is first described by Dr. James Parkinson's in 1817 as a "shaking palsy." It is Characterized by motor and non-motor symptoms including hallucination, depression, bradykinesia, sleeping disorder etc... Various other signs and symptoms are shown. Genetic factors, environmental factors can cause Parkinson's disease which affect the dopamine release in the brain. To control the symptoms of Parkinson's disease various medication are available but levodopa are more common. Levodopa are given with carbidopa combination in which levodopa get convert into dopamine and then activate the post synaptic dopaminergic receptors and give the relax in Parkinson's diseases symptoms.

Keywords: Parkinson's disease, Levodopa, Dopamine agonist

INTRODUCTION

Parkinson's Disease is a progressive neurodegenerative disease diagnosed by bradykinesia, rigidity and tremor with postural disability seen in some patients as the disease at an advanced stage with significant morbidity and mortality. It was first described by Dr. James Parkinson in 1817 and further innate by Jean- Martin Charcot. [1,2]

Parkinson's disease is the most common disorder after Alzheimer's disease with the frequency: [1]

- 0.5-1% are old 65-69 year of age
- 1-3% are of 80 year of age and older

By ageing the population, the range of Parkinson's disease increase by more than 30% by 2030.[1]

The main indication of Parkinson's Disease is motor symptoms, but it is also associated with non-motor symptoms along with depression, autonomic dysfunction and hallucinations which cause initial difficulties in diagnosis of Parkinson's Disease. Motor symptoms lead to treatment with levodopa/carbidopa, monoamine oxidase-B inhibitors and non-ergot dopamine agonists. Levodopa can cause dyskinesias and motor symptom fluctuation or malfunctioning by the long-term use and high dose taken. [2]

Early symptoms of Parkinson's disease are following:

- Disability in movement & balancing of the body
- Problem with smelling
- Voice tone change
- Smaller handwriting
- Insomnia
- Face expression change because of change in nerves that control face muscles
- Mood swings
- Difficulty in eating
- Hallucinations [6]

Table 1: Sign & Symptoms [3]

Motor Skill Symptoms
• Bradykinesia
• Vocal Symptoms
• Rigidity and postural instability
• Tremors
• Walking or Gait Difficulties
• Dystonia
Non-Motor Skill Symptoms
• Mental/Behavioural issues
• Sense of smell
• Sweating and melanoma
• Gastrointestinal issue
• Pain

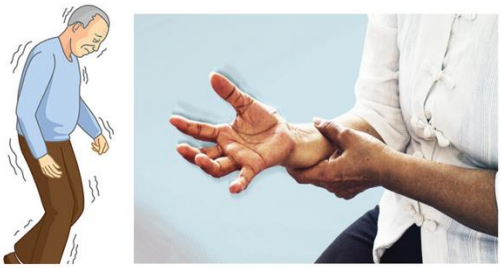


Figure 1: Parkinson's Disease Symptoms [4, 5]

Etiology

Parkinson's disease occurs when nerve cells or neurons present in brain gently break down or dead because of losing neuron that are response for the release of chemical messenger known as Dopamine. When dopamine levels decrease in the brain cause abnormally and shows the many of symptoms of Parkinson's disease.

Basically, Parkinson's disease causes are still unknown, although various factors are shown including:

- Genetic mutation
- Lethal environmental
- Dopamine release disorder [7]

Table 2: Risk factor co-related with Parkinson's disease [8-25]

• High cholesterol
• Environment toxicity (Cyanide, Herbicides, Pesticides, carbon disulfide, methanol and organic solvents)
• Nitric oxide toxicity
• Oxidative Stress (formation of free radicals)
• Brain injury
• Mitochondrial disorder
• High calories consumption
• More body mass index
• Post-infection states
• Signal-mediated apoptosis

Table 3: Gene Mutations co-related with Parkinson's disease [9-25]

• Alpha-synuclein gene (SNCA)
• Eukaryotic translation initiation factor 4 gamma 1 gene (EIF4G1)
• Superoxide dismutase 2 gene (SOD2)
• Vacuolar Protein Sorting

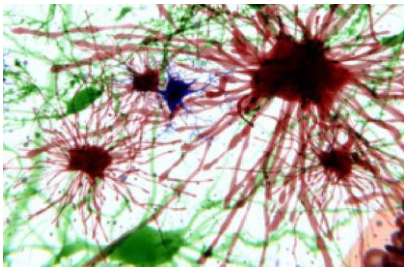
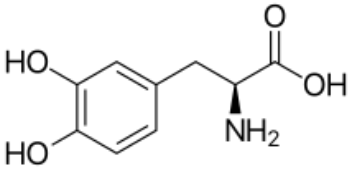


Figure 2: Dopamine release [26]

Medication

Vast advancement has been made in the treatment of Parkinson's disease over past century, although levodopa is more potent drug for controlling Parkinson's disease symptoms. Treatments can vary from drugs, therapy, surgeries, and combination of different treatment. Each patient's therapy should be individual and other than levodopa many other drugs are present for the drug therapy such as dopamine agonists catechol-o-methyltransferase inhibitors and non-dopaminergic agents [27, 28].

Levodopa is the most successful indicative treatment of Parkinson's disease [29]. Oral levodopa has been widely used for over 40year with the combination with dopa-decarboxylase inhibitors (DDCI) which decrease the treatment complication, extending its half-life and bioavailability increase in the brain. Catechol-o-methyl-transferase (COMT) inhibitors can also use to improve bioavailability of levodopa [30].



Structure 1: Levodopa [31]

Mechanism [32]

- Levodopa converts into dopamine in CNS and Periphery both
- Increase the bioavailability of levodopa
- Administered in combination with peripheral decarboxylase inhibitors (carbidopa and benserazide).
- Dopamine decarboxylase inhibitors prevent levodopa for converting into dopamine in periphery.
- Permit levodopa to cross blood-brain barrier.
- Then, dopamine activate post synaptic dopaminergic receptors.

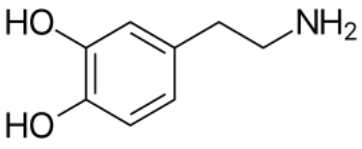
Adverse drug reaction [33]

- Dizziness
- Dry mouth
- Chest pain
- Depression
- Confusion
- Hallucination
- Blood in stool
- Abdominal pain
- Blood in vomit
- Body weakness
- Regular heartbeat
- Fever
- Nausea
- Redness, swelling, pain, or warmth in the area around PEG-J tube (if levodopa and carbidopa suspension administered)

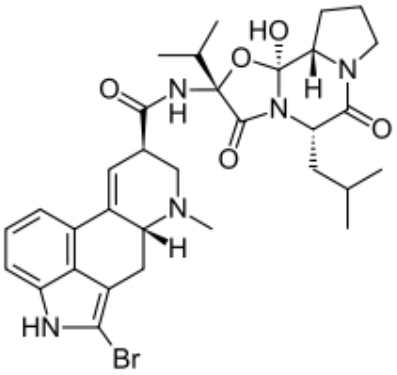
Figure 3: Chest pain [34]

Figure 4: Hallucination or confusion [35]

Dopamine Agonists are most commonly therapeutic agent used in the treatment of Parkinson's disease through reducing the undesired motor fluctuation and delay the administration of levodopa. These therapeutic agents are chemical compounds that binds to dopamine receptors when endogenous neurotransmitter dopamine are not present. Some first line drug for the treatment is bromocriptine (BRC) and cabergoline (CAB). [36, 37]



Structure 2: Dopamine Agonists [38]



Structure 3: Bromocriptine [39]

Mechanism [40]

Dopamine agonist act on dopamine receptors that are 7-transmembrane domains and members of GPCR superfamily(G-protein-coupled receptors). Dopamine receptors are D1, D2, D3, D4 and D5, these receptors are subdivided on the basis of mechanism of action on adenylate cyclase enzyme i.e. D1 like receptors are D1 and D3 and D2 like receptors are D2, D3 and D4.

Whereas, D1 like receptors are first bind with $G\alpha_{s/olf}$ protein and increase cAMP level in intracellular by activating adenylate cyclise and also activate $G_{\beta\gamma}$ complex and N-type Ca2+ channel. D2- like receptors inhibit adenylate cyclase so that second messenger cAMP is decrease in intracellular level.

Adverse drug reaction [41]

- Nausea
- Headaches
- Vomiting
- Orthostatic hypotension
- Suppress milk production
- Pulmonary fibrosis (overdose of bromocriptine)

Figure 5: Orthostatic hypotension [42]

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