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Review Article

PARKINSON'S DISEASE: CLINICAL PRESENTATION AND MANAGEMENT

Parle Milind *, Rakha Pankaj
Pharmacology Division, Dept. of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar, Haryana, India
*Corresponding author Email: mparle@rediffmail.com

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ABSTRACT

James Parkinson described a disease called shaking palsy in 1817, which showed clinical signs of muscular rigidity, poverty of movements, postural imbalance and resting tremors. The pathological hallmark of PD is loss of dopaminergic neurons of the substantia nigra pars compacta, with the appearance of intracellular inclusions known as Lewy bodies. We find mention of Kampavatta a disorder resembling Parkinsonism in ancient Charak Sanhita also. Levodopa, the metabolic precursor of dopamine, is the single most effective agent in the treatment of PD. levodopa is almost always administered in combination with a peripherally acting inhibitor of aromatic L-amino acid decarboxylase, such as carbidopa or benserazide. Levodopa therapy can have a dramatic effect on all the signs and symptoms of PD. An alternative to levodopa is the use of drugs such as Bromocriptine, Pergolide, Ropinirole and Pramipexole. The therapeutic action of the COMT inhibitors is to block peripheral conversion of levodopa to 3-*O*-methyl DOPA. A recently developed class of drugs for the treatment of PD consists of inhibitors of COMT like Tolcapone and Entacapone. MAO-B is the predominant form in the striatum and is responsible for most of the oxidative metabolism of dopamine in the brain. Therefore, Selegiline the selective irreversible inhibitor of enzyme MAO-B also find a place as an effective anti-parkinsonian agent. The present review focuses on clinical signs, symptoms and drug therapy of PD in detail. At present, the pharmacological therapy of neurodegenerative disorders is limited mostly to symptomatic treatments that do not alter the course of the underlying disease.

Keywords: Dopamine, Lewy body, biomarker, neurodegenerative.

INTRODUCTION

Parkinson's Disease (PD) is an extremely common (second most common neurodegenerative disorder next to Alzheimer's disease) debilitating disorder[1, 2]. It affects approximately 1 % of the population over the age of 60 around the world. In addition, about 50,000 individuals are diagnosed with PD each year and there is no gender preference[3]. Clinical treatment suffers from the fact that definitive diagnosis is not possible pre-mortem since; there is no sure shot diagnostic test available. PD is characterized by the progressive loss of dopaminergic neurons in the substantia Nigra of midbrain[4]. These neurons project widely through out the cereberal hemispheres but the motor symptoms of PD such as bradykinesia, rigidity, resting tremors, loss of balance and slowness are due to loss of dopaminergic nerve terminals in the caudate and putamen nuclei of the basal ganglia. However, besides the dopaminergic deficit, PD is now believed to be a multicentric neurodegenerative disease. Biomarkers for the Parkinson's disease have been identified which can be detected in blood, serum and plasma in addition to urine and CSF. The induction of alpha-synuclein expression as a specific disease biomarker in PD skin fibroblasts has been reported[5]. Clinically, it is a movement disorder and the neuropathological hallmark of PD is the cytoplasmic accumulation of fibrous proteins in the brain cells which are called as Lewy bodies. These are found in the degenerating neurons and comprise of neurofilaments with aggregated alpha synuclein and ubiquitin immunoreactivity. Whether Lewy bodies are causative or symptomatic in PD pathogenesis is not clear. However, the latter appears to be the case in all probability. It has been suggested that these deposits are responsible for the degeneration of neurons containing Dopamine.

History

James Parkinson described a disease called shaking palsy or paralysis agitans in 1817, which exhibited symptoms such as muscular rigidity, bradykinesia and slow movements. Initially, this disorder was called as Parkinson's syndrome which later on became popular as Parkinson's disease with advancement in biomarker detection and technology. In 1912, Friedrich Heinrich Lewy first described the cytoplasmic accumulation of fibrous proteins in the brain cells which are called as Lewy bodies that are now seen as pathologic hallmark of idiopathic PD[6]. There is a loss of pigmented cells (dopaminergic neurons) in the substantia nigra pars compacta in patients with the encephalitic form of PD[7]. In 1950's Carlson observed that majority of the brain dopamine content is localized in the basal ganglia [8]. He found a direct link between deficiency of Dopamine and development of Parkinsonian symptoms. The post mortem biochemical analysis confirmed depletion of Dopamine levels in brain areas such as nucleus caudatus, putamen, nucleus accumbens, Substantia Nigra and globus pallidus of patient suffering from Parkinson's Disease[9].

Clinical presentation of Parkinson's disease

The neuropathological examination is the only tool available for PD. The Biological markers for the Parkinson's disease can be found in blood, serum, plasma, urine and CSF. The autopsy studies showed incorrect results in about 24 percent of cases[10].

PD can be differentiated from Parkinsonism due to other disorders via symptoms and signs, resting tremor, and good response to Levodopa. The occurrence of the 4-to-6-Hz tremor at rest in other Parkinsonian disorders makes this a useful differentiating feature and it is also absent in up to one quarter of cases of Parkinson's disease[11]. It is important to differentiate between PD and Parkinsonism due to other diseases, to establish the proper treatment and prognosis of the disease. In elderly patients the important feature for the disease is Dementia[12]. The literature reveals that the patients suffering from PD have their lives short due to presence of Dementia[13]. PD is characterized by the progressive death of selected but heterogeneous populations of neurons. Every dopaminergic projection area is not equally susceptible. In the area substantia nigra pars compacta, neuronal loss tends to be greatest in the ventrolateral tier (loss is estimated to be 60 to 70 percent at the onset of symptoms), followed by the medial ventral tier and dorsal tier. It results in a loss of striatal dopamine, most prominently in the dorsal and intermediate subdivisions of the putamen[14], which is the main reason for akinesia and rigidity. This pattern of cell loss also correlates with the degree of expression of messenger RNA for the dopamine transporter[15]. The greater loss of medial nigral cells, with projections toward caudate nucleus, result in more cognitive dysfunction[16].

The diagnosis of Parkinson's disease is based on the presence of bradykinesia, akinesia and tremor when the limb is at rest/ rigid or both[17]. Parkinson's disease is characterized by a resting tremor in a limb, most commonly one hand that disappears with voluntary movement. The diagnosis of the PD is found to be complicated by non-classic findings, such as tremor when the person is holding the arms out or using the hands in voluntary movement or the absence of a tremor[18]. The bradykinesia in patients begins asymmetrically in about 75 percent of patients. Patients may notice difficulty while getting out of cars, rising from deep chairs, and rolling over in bed. However, a shuffling gait, freezing, and falls are rare in early disease. Shuffling gait disorders with other causes were the second most common misdiagnosis of Parkinson's disease in general practice[19]. There are no laboratory tests or imaging studies that confirm the diagnosis. MRI of the brain may be appropriate in patients, with more gait abnormalities, to exclude other conditions, but are necessary in a typical case. The causes of Parkinsonism are toxins, infections of the CNS, structural lesions of the brain, metabolic disorders, and other neurologic disorders Drug-induced Parkinsonism is important to recognize because it is reversible, although reversal may require weeks or months. Some classes of drugs like Dopamine antagonists, atypical neuroleptic agents, antiemetic drugs, calcium channel antagonists may also cause Parkinsonism, but the mechanism is uncertain. Parkinsonian symptoms can be found in 25 percent of patients who received an initial clinical diagnosis of Parkinson's disease. The other conditions include falls or dementia early in the course of the disease, wide-based gait, abnormal eye movements, Babinski signs (Toes fanning out / inward), marked orthostatic hypotension and urinary retention. The awareness for Hyposmia is very poor in case of PD patients. Disturbed sleep- including shouting out, failing movements of arms and legs, and falling off the bed during dreaming—might only be noticed if the patient's spouse is specifi cally questioned. These symptoms suggest rapid eye movement (REM) sleep disorder and can be treated with clonazepam[20].

Management of PD

Being diagnosed with PD can be frightening and cause worry, anger, sadness and other emotional disturbances. In the present review the drug therapy and non-drug management approaches have been discussed.

Levodopa

The precursor of Dopamine is Levodopa. It is the single effective drug in the treatment of PD. The therapeutic and adverse effects of the drug are due to the decarboxylation of Levodopa to Dopamine. Levodopa is an inert drug. On oral administration, it is absorbed rapidly from small bowel. The peak concentration of drug in plasma can be seen after 0.5 to 2h after oral administration. The plasma half life of the drug is short. Various factors on which rate and extent of absorption depends are gastric emptying, the pH of gastric juice, and the length of time the drug is exposed to the degradative enzymes. If the drug is administered with meals it delays absorption and reduces peak plasma concentrations. The passage of drug across blood brain barrier is mediated by a membrane transporter and a competition between proteins and the drug occur at this level. The dopamine produced is responsible for the therapeutic effectiveness of the drug in PD after release and it is either transported back into dopaminergic terminals by the presynaptic uptake mechanism of MAO and COMT.

Levodopa is always administered with Carbidopa or Benserazide that don't penetrate into the CNS. If the drug is administered alone, the drug gets decarboxylated by the enzymes in mucosa and other peripheral sites. The dopamine released into circulation by the conversion of levodopa produces nausea. Inhibition of peripheral decarboxylase enzyme increases the amount of levodopa that remains unmetabolized and available to cross the blood brain barrier. It reduces the incidence of gastrointestinal side effects. In most individuals, a daily dose of 75 mg carbidopa is sufficient to prevent the development of nausea. For this reason, the most commonly prescribed form of carbidopa/levodopa is the 25/100 form, containing 25 mg carbidopa and 100 mg levodopa[21].

The therapy of Levodopa has a very promising effect on all the signs and symptoms of the disease. The improvement factor in tremor, rigidity and bradykinesia is near to completion in the early stage of the disease. However, long term use of levodopa affects the motor state of the patient by fluctuations in motor behavior.

"Wearing off phenomenon is another problem associated with this therapy. Each dose of levodopa effectively increases the mobility for a period of 1 to 2 hours, but rigidity and akinesia return rapidly at the end. This situation can be improved by increasing the dose and frequency of administration.

When the plasma concentration of levodopa is high, dyskinesia can be seen a number of times, although in some patients, dyskinesia or dystonia may be provoked when the level is rising or falling. Like akinesia and rigidity, the dyskinesia movements are also uncomfortable. During the later stage of the disease the patients may feel fluctuations rapidly between being "off" with no beneficial effects and being "on" but with dyskinesias. This situation is properly known as on/off phenomenon[22].

The evidences indicate that the on/off phenomena and dyskinesias may be the result of an active process of adaptation to variations in brain and plasma levodopa levels. This process involves not only alterations in the function of dopamine receptors but also includes downstream changes in the postsynaptic striatal neurons including modification of NMDA glutamate receptors[23].

Other than motor fluctuations and nausea, adverse effects like hallucinations and confusion. These types of adverse effects are more common in elder patients who are already suffering from dementia. It always limits the treatment pattern. Phenothiazines like drugs are very much effective against psychosis induced by

levodopa but they cause worsening of PD due to D2 receptor action. Now a days drug like clozapine and quetiapine which act as atypical antipsychotic are used because they do not worsen the symptoms of PD but have a remarkable effect on psychosis[23].

Dopamine-Receptor Agonists

These medications are used as an alternate to levodopa because these drugs are direct agonists of striatal dopamine receptors. This approach has several potential advantages, since enzymatic conversion of these drugs is not required for their action and their action does not depend on nigrostriatal neurons. These drugs have longer duration of action than Levodopa and are used in managing the patients on dose-related fluctuations in motor state. The literature on these drugs states if the hypothesis that the free radicals which are formed as a result of dopamine metabolism contributes to the cell death than these drugs have the potential to reduce the release of dopamine and thereby modify the course of the disease. Bromocriptine and pergolide are the older drugs from this category, while the other two drugs ropinirole and Pramipexole are newer compounds added to the list. Bromocriptine and pergolide both are ergot derivatives and show a similar therapeutic actions and adverse effects.

Bromocriptine is an agonist of the D2 class of dopamine receptors and a partial antagonist of the D1 receptors, whereas pergolide is an agonist of both classes. Ropinirole and pramipexole have selective activity at D2 class sites with little or no activity at D1 class sites. All of these drugs are well absorbed by oral route and show same therapeutic actions. The duration of action of the dopamine agonists (8 to 24 hours) often is longer than that of levodopa (6 to 8 hours) as discussed earlier and so they are useful in patients with on/off phenomena. These drugs like Levodopa can also produce hallucinosis or confusion and may worsen the orthostatic hypotension. The newer analogues of this class are more tolerable by the patients as compared to the older drugs. Initial treatment with this class of drugs may cause profound hypotension, so they should be started at a very low dose. Symptoms of nausea and fatigue are shown with these drugs, but they require slow adjustment of the dose. Ropinirole and Pramipexole are the drugs which can achieve therapeutically useful doses in a week or less. They tend to lower gastrointestinal disturbance, but they can produce nausea and somnolence. The literature reveals the fact that somnolence in some patients is quite severe which can lead to sudden attacks of irresistible sleepiness which lead to motor vehicle accidents. If somnolence is seen in patients than it is better to switch the patient to another treatment. Recent literature also implies that long term use of pergolide can also induce cardiac valvular disease. If these reports of the cardiac valvular disease are confirmed than the patient may be given nonergot agents[24]. The introduction of pramipexole and ropinirole (the newer compounds of this category) has increased their use in patients suffering from PD, because these selective agonists are well tolerated and they are used as initial treatment for PD rather than as adjuncts to levodopa. This is due to following reasons: (1) Due to longer duration of action these agents may not induce on/off effects and dyskinesias (2) because levodopa may give rise to oxidative stress, which will kill dopaminergic neurons[25].

Apomorphine

It is a dopaminergic agonist and is given by subcutaneous injection. It has very high affinity for D4 receptors, moderate affinity for D2, D3, D5, and adrenergic α1D, α2B, and α2C receptors; and low affinity for D1 receptors. This drug is a powerful emetic, so it requires pre and post anti-emetic therapy with it. This is due to this adverse effect that use of this drug is particularly their when other drugs such as oral dopamine agonists or COMT inhibitors, have failed to control the "off" episodes.

Catechol-O-Methyltransferase (COMT) and Mono Amine Oxidase (MAO) Inhibitors

These two classes are newer choice of the drugs for the patients suffering from PD. Dopamine and levodopa are both catabolized with the help of these drugs. COMT produces the pharmacologically inactive compounds 3-O-methyl DOPA (from levodopa) and 3-methoxytyramine (from dopamine). When levodopa is administered orally, nearly 99% of the drug is catabolized and does not reach the brain. Most of the drug is converted by aromatic L-amino acid decarboxylase (AAD) to dopamine, which causes nausea and hypotension. Carbidopa helps to reduce the formation of dopamine but increases the fraction of levodopa that is methylated by COMT. The mechanism of action of COMT inhibitors is to block the conversion of levodopa to 3-O-methylDopa in the periphery which increases the plasma half life of the drug. The common adverse effects of these agents are nausea, orthostatic hypotension, vivid dreams, confusion, and hallucinations. Another important adverse effect associated with tolcapone is hepatotoxicity.

Two isoenzymes of MAO are found. Both of these isoenzymes (MAO-A and MAO-B) are present in the periphery and inactivate monoamines of intestinal origin. The isoenzyme MAO-B is mainly found in the striatum and is responsible for most of the oxidative metabolism of dopamine in the brain. Selegiline is a selective inhibitor of MAO-B, leading to irreversible inhibition of the enzyme[26]. Selegiline does not inhibit peripheral metabolism of catecholamines, so it can be taken safely with levodopa. At higher dose Selegiline can produce inhibition of MAO-A and should be avoided. The basis of the efficacy of selegiline is presumed to be its capacity to retard the breakdown of dopamine in the striatum. The literature states that the ability of selegiline to slow the metabolism of dopamine is an important reason behind its neuroprotective properties.

Muscarinic Receptor Antagonists

Antagonists of muscarinic acetylcholine receptors were used widely for the treatment of PD before the discovery of levodopa. The biological basis for the therapeutic actions of these drugs is not completely understood, but they act within the neostriatum through the receptors which mediate the response to intrinsic cholinergic innervation of this structure is their prime action[27].

Amantadine

It is not clear that which properties of this drug are responsible for its antiparkinsonian actions. It appears to alter dopamine release in the striatum and also has anticholinergic properties. The most significant action of amantadine is its ability to block NMDA glutamate receptors[28]. In any case, the effects of amantadine in PD are modest. It is used as initial therapy of mild PD. Adverse effects of Amantadine include Dizziness, lethargy and sleep disturbance in addition to nausea and vomiting. These adverse effects if produced in patients are always mild and reversible.

Neuroprotective Treatments for Parkinson's Disease. It would be desirable to identify a treatment that modifies the progressive degeneration that underlies PD rather than simply controlling the symptoms[29]. Some of the strongest evidence for a neuroprotective

action has emerged from long-term studies of the effects of the dopamine agonists pramipexole and ropinerole.

Non-Drug Therapy

In the present section, apart from medical treatment, strategies have been pointed out for non-drug therapy of the disease to improve the quality of life of patients suffering from PD:

1. How exercise is helpful?
Exercise can help the people with PD improve their mobility and flexibility. It can also help prevent complications like Joint pain that can be caused by the symptoms of the disease. The exercise program help patient feel more confident and in control of their disease. A physical therapist can help develop an exercise program that can fit an individual's needs and abilities. An exercise program can offer many benefits to the patients viz. Increasing the strength, improving stamina, optimizing the coordination, decreasing the rigidity, improving flexibility and delaying the progression of the disease.

2. Importance of stress management
Neurodegenerative disorders have a natural tendency to evoke depressive symptoms. Therefore, stress management and depression management are recommended for all elderly patients above 60 years of age whether suffering or not form any neurological or psychiatric disorder. Stress management helps the patient to relieve the symptoms as the patient becomes irritated or feel loneliness.

3. Family support at home
The support of family is a prime tool in managing the disease as family members play an active role in the life of patients. If the patient has a support within the family, he/she can counterbalance the symptoms of the disease very easily.

4. Support at office (Occupational therapist and friends)
An occupational therapist can help the patient carry out their daily activities more comfortably and safely. The therapist can visit the home and help in making the home safer for the patient by using handrails, banisters, grab bars, tub rails and elevated toilet seats. Some therapists can also evaluate the driving skills of the patient as it is a motor disorder and help the patient in determining if the disease is affecting a person's ability to drive safely or not.

5. Dietary measures
Patients suffering from PD does not require to eat a specific diet but getting enough diet will help maintain he muscle and bone strength. Later in the disease, changes may have to be made to the diet because of swallowing difficulties. These may include a diet of soft or chopped foods or liquids. It is important to look after your weight because the motor symptoms get worsen during the disorder. Malnutrition can worsen the symptoms of the disease.

Table 1: Different drugs available in the market with special Remarks

Medicine	Brand name	Manufacturer	Dosage form available	Dose	Adverse effects	Remarks
Levodopa/ Carbidopa	SYNDOPA 275 AND 110	Sun pharma	275 mg tabs and 110 mg tabs	1 tab 3-4 times daily with increment of 1 tab every 1-2 days up to a max of 8 tabs daily	Anorexia, postural hypotension, depression, insomnia, blepharospasm	Used as adjuvants therapy
B romocriptine	SICRIPTIN	Serum	1.25 mg, 2.5 mg tabs	Week 1-1.25 mg at bed time Week 2- 2.5 mg at bed time Week-3- 2.5 mg twice daily Week-4- 2.5 mg three times daily	Drowsiness, vasospasm, syncope, asthenia	Used in patients with severe early morning disability
Pergolide	PERLIDE	Chemech	0.05mg tabs	50 µg daily taken as single dose and then 50 µg twice daily on days 2-4 and increasing to 1.5 mg daily in three divided doses	Dysponea, diplopia,, cardiac fibrosis	Act by stimulating surviving dopamine receptors
Ropinirole	ROPITOR	Torrent	0.25 mg, 0.5 mg, 1 mg, 2 mg tabs	Week 1-0.25 mg three times daily Increasing 0.25 mg every weak up to 1 mg daily	Pharingitis, athralgia	Used as monotherapy in younger patients where there is risk of long term side effects
Pramipexole	PRAMIPEX	Sun pharma	0.25 mg and 0.5 mg tabs	0.125 mg three times daily and doubling the dose every 5-7 days to 0.5 mg three times daily	Hypertonia and peipheral oedema	Alone or with levodopa for treatment of idiopathic PD
Selegilline	SELGIN	Intas	5mg tabs	10 mg daily either as single dose or in divided doses up to lunch	Vivid dreams, myopathy	It is used with levodopa to reduce end of dose deterioration
Trihexphenidyl	PACITANE	Wyeth	2 mg tabs	1 mg first day, 2 mg second day then increase 2mg daily every 3-5 days	Blurred vision and euphoria	Tradive dyskinesia
Amantadine	AMANTREL	Cipla	100mg caps	100 mg daily for 1st week, increasing to 100 mg twice daily	Neuroleptic malignant syndrome	Thought to enhance dopamine availability

CONCLUSION

Neurodegenerative disorders are characterized by irreversible progressive loss of neurons from the specific area of the brain. The pathogenesis of PD has not been fully elicited and the disease may have multiple causes including genetic risk, environmental factors and overuse of psychotropic drugs. The motor impairment of PD arises from selective loss of Dopaminergic neurons in the substantia nigra pars compacta. Levodopa the metabolic precursor of dopamine, is the single most effective agent in the treatment of PD. Dopaminergic stimulation accounts for Levodopa's adverse effect. Thus, Levodopa can cause Nausea, Vomiting, Postural hypotension and rarely arrhythmias. Sedation, vivid dreams, nightmares and hallucinations occur as dose related side effects especially in elderly patients with cognitive decline. Ayurveda described several formulations for the treatment of Kampavata. At present, the pharmacological therapy of neurodegenerative disorders is limited mostly to symptomatic treatments that do not alter the course of the underlying disease. Symptomatic treatment for PD, where the neurochemical deficit produced by the disease has been well defined, is in general, relatively successful, and a number of effective agents are available *viz* Dopaminergic agonists, COMT inhibitors and MAO-B inhibitors.

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