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REVIEW ARTICLE ON PARKINSON DISEASE

Rabia Choudhary*[1] and Dr. Satish Sharma

[1]Sunder Deep Pharmacy College 201015 Ghaziabad.

Dr. A P J Abdul Kalam University Lucknow (UP).

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***Corresponding Author**
Rabia Choudhary
Sunder Deep Pharmacy
College 201015 Ghaziabad.

ABSTRACT

Parkinson disease is a neurodegenerative disorder characterised by the cardinal symptoms of stiffness, resting tremor, slowness (bradykinesia) and reduction of movement (hypokinesia). It is an aging population and although there have been several significant breakthroughs in terms of the treatment of this debilitating disease, such as drugs levodopa, dopamine [DA] agonists, anticholinergics and surgery (deep brain stimulation, transplants). Parkinson's disease is a chronic, progressive, neurodegenerative disorder with an estimated prevalence of 31 to 328 per100, 000 people worldwide. It is estimated that more than 1 percent of the population over age 65 are afflicted with Parkinson's disease, incidence and prevalence increase with age. several models are used in Parkinson disease like neurotoxin models MPTP, 6-OHDA and Pesticides and herbicides models like Paraquat and Rotenone. Antioxidants play a essential role in the prevention or treatment of Parkinson disease, three main antioxidant suppliments are tocopherol, CoQ10, and glutathione.

KEYWORDS: Parkinson Models, MPTP, 6-OHDA, Paraquat, Rotenone, and Anti parkinson drugs.

INTRODUCTION

Parkinson Disease is a disorder of the central nervous system, involving primarily a degeneration of certain nerve cells in deep parts of the brain called the basal ganglia, and in particular a loss of nerve cells (or neurons) in a part of the brainstem called the substantia nigra. These cells make the neurochemical messenger dopamine, which is partly responsible for starting a circuit of messages that coordinate normal movement.[1] Parkinson's disease is a chronic, progressive, neurodegenerative disorder with an estimated prevalence of 31 to 328 per 100,000 people worldwide. It is estimated that more than 1 percent of the population over

age 65 are afflicted with Parkinson's disease, incidence and prevalence increase with age.[2] Three main antioxidant suppliments are tocopherol, CoQ10, and glutathione are play a essential role to prevention or treatment of parkinson disease. These agents have been studied because of their potential to alter the course of 2 common theories of Parkinson disease pathogenesis free radical generation and mitochondrial complex-1 deficiency. The literature search revealed 3 large clinical studies of tocopherol (2 observational, 1 prospective randomized), 4 trials of CoQ10, and 1 study of glutathione. With the exception of the large observational studies with tocopherol and one study of CoQ10 that enrolled 80 patients, each of the other studies retrieved included fewer than 30 patients were conducted for 3 months or less. Antioxidant supplementation, in particular tocopherol, did not appear to alter the course of parkinson disease. However, in 2 of the studies of CoQ10 and in the study of glutathione, a small but statistically significant improvement in Parkinson disease symptoms was observed. At present, antioxidants and supplements appear to have a limited role in the prevention or treatment of Parkinson disease. CoQ10 appears to provide some minor treatment benefits. More study is necessary to determine whether CoQ10 has a significant role as primary or adjunctive therapy in Parkinson disease.[3] Although no drug has yet been established to alter the rate of disease progression, recent publications have confirmed previous results and hypotheses about the probable role of thiolic antioxidants on Parkinson's disease, demonstrating a significant reduction of dopaminergic neuronal degeneration in a-synuclein over expressing mice treated with oral N-acetyl-cysteine. This thiolic antioxidant is a modified form of the natural amino acid cysteine, which is the precursor of the most potent intracellular antioxidant glutathione. Besides, increasing evidence has been accumulated in the last 10 years about the beneficial effects of this thiolic antioxidant in experimental and pathologic states of the nervous system, including against neurotoxic substances. The N-acetyl-cysteine used to alone or in combination with levodopa in the clinical management of this neurodegenerative disorder.[4] Parkinson's disease is a progressive neurodegenerative disease in the elderly, and no cure or disease-modifying therapies exist. Several lines of evidence suggest that mitochondrial dysfunction and oxidative stress have a central role in the dopaminergic neurodegeneration of Parkinson's disease. In this context, mitochondria-targeted therapies that improve mitochondrial function may have great promise in the prevention and treatment of Parkinson's disease.[5] Oxidative stress is play a central role in the pathogenesis of Parkinson's disease in which neurons are highly susceptible, is also known to induce oxidative changes in human red blood cells in vivo and in vitro. We have undertaken this study to ascertain the possibility of oxidative damage to the RBCs in PD by measuring

the cytosolic antioxidant enzymes viz., superoxide dismutase, catalase, glutathione peroxidase and glucose-6-phosphate dehydrogenase. The SOD, CAT, G-Px and G6PD activities were significantly lower in patients with PD compared to the control. A significant (P<0.05) negative correlation of enzyme activities with Hoehn and Yahr stage of the disease.[6]

PATHOPHYSIOLOGY

The basal ganglia and midbrain involved in the control of movement. They include the striatum, mainly comprising the caudate and putamen, the globus pallidus, the subthalamic nucleus, and the main pigmented component of the substantia nigra known as the pars compacta.[7] The clinically important motor circuit originates in the sensorimotor cortex and terminates in the supplementary motor area. The middle part of the loop divides into two pathways from striatum to thalamus. There is a one station direct pathway via the internal part of the pallidum and a three station indirect pathway via the external globus pallidus, the subthalamic nucleus and the internal globus pallidus. he nigrostr Lang.[8] Tiatal pathway projects from the substantia nigra pars compacta to the striatum, where it makes two kinds of synapses on the projection neurones. Those upon direct pathway neurones are facilitatory via dopaminergic type 1(D1) receptors on the dendritic spines, and those upon indirect pathway neurones are inhibitory via D2 receptors. Cholinergic internuncial neurones are excitatory to projec- tion neurones and are inhibited by dopamine. In Parkinson's disease, acetylcholine is present in normal amounts in the striatum. However, dopamine defciency produces imbalance in the dopamine: acetylcholine ratio, thereby aggravat- ing the symptoms of Parkinson's disease. A healthy substantia nigra is tonically active, favouring activity in the direct pathway. Facilitation of the direct pathway is necessary for the supplementary motor cortex to become active before and during movements. Parkinson's disease is characterized by a loss of dopaminergic neurones in the substantia nigra of the basal ganglia.[9] A decrease in dopamine production results in facilitation of the indirect pathway because of a lack of D1 facilitation of the direct pathway and of D2 inhibition of the indirect pathway. This dopamine is associated with increased activity of inhibitory nuclei in the basal ganglia (using the neurotransmitter g-aminobutyric acid (GABA)), eventually leading to excessive inhibition, and effectively to a shutdown, of the thalamic and brainstem nuclei that receive from the basal ganglia. Excessive thalamic inhibition results in suppression of the cortical motor system with akinesia, rigidity and tremor, while inhibition of brainstem locomotor areas may contribute to abnormalities of posture and gait.[8]

SYMPTOMS

Symptoms usually appear after the age of 50. The mean age at onset is 55-75 years in both sexes. The young are no except and onset before age of 30 does not preclude a diagnosis of Parkinson disease.[9]

Motor symptoms

A. Cardinal symptoms

- **Tremor:** Tremor is defined as rhythmic oscillation of a body part. There are more than 20 kinds of tremor. The most useful distinction is between resting and action tremors. Rest tremor occurs when a body part, such as hand is not in use. Typical rest tremor has frequency of 3 to 6 cps and will disappear with any movement, even a simple change in
- position.[10]
- **Rigidity:** Stiffness, increased muscular tone. In combination with resting tremor, this produces ratchety, "cog wheel" rigidity when the limb is passively moved.
- **Bradykinesia/akinesia:** Respectively, slowness or absence of movement.
- **Postural instability**: Failure of postural reflexes, which leads to impaired balance and falls.[11]

B. Other motor symptoms

- Gait and posture disturbance, Shuffling, Decreased arm swing.
- Difficulty in turning head. Stopped, forward – flexed posture.
- Festination – combination of stooped posture, imbalance.
- Dystonia (In about 20% of cases)– Abnormal, sustain, painful twisting muscle contractions, usually affecting the foot and ankle.
- Speech and swallowing disturbances, Hypophonia – soft speech.
- Festinating speech –excessive rapid, poorly intelligible speech
- Speech/language disturbance– less verbal fluency, cognitive disturbance.
- Dysphagia –impaired ability to swallow, Fatigue (up to 50% cases).
- Masked faces, with infrequent blinking.
- Difficulty rolling in bed or raising from seated position.
- Micrographia (small, cramped hand writing).
- Impaired motor coordination, Poverty of movement.

Non – motor systems

- Mood disturbances, Depression (20-80% cases), Anxiety.

- Cognitive disturbance, Slowered reaction time, Executive dysfunction.
- Dementia, Short term memory loss, Sleep disturbances
- Daytime somnolence, Disturbances in REM sleep, Sensational disturbances
- Impaired visual contrast sensitivity, Dizziness, Reduction or loss of sense of smell, Pain.[12]

The neurotoxin models

Several toxic animal models are used in primates and rodents with the exception of 6-hydroxydopamine (6-OHDA) and MPTP, these models are based on pesticide. They have opened crucial doors to increase our knowledge base of the events that may lead to the Parkinson disease neurodegenerative process.

6-Hydroxydopamine Model

It is the classic animal model of Parkinson disease. This compound does not cross the blood–brain barrier which necessitates its direct injection into the substantia nigra pars compacta (SNpc) or the striatum. Injection of 6-OHDA into the SNpc, as first demonstrated by Ungerstedt in 1968[13], knocks out about 60% of the tyrosine hydroxylase (TH)-containing neurons in this area of the rat/mouse brain, with the subsequent loss of the TH-positive terminals in the striatum.[14] Several researchers have injected this compound directly into the striatum to study retrograde degeneration because it is believed and it has been demonstrated that the TH-positive terminals here die prior to the TH-positive neurons in the SNpc which seems to be a replicate of the PD picture.[15] 6-OHDA uses the DA transporter to gain access to the cytosol where it can auto-oxidize, hence generating an intracellular oxidative stress. Although 6-OHDA does not produce or induce proteinaceous aggregates or Lewy-like inclusions like those seen in PD, it has been reported that 6-OHDA does interact with alpha-synuclein.[16] 6-OHDA is best used as a unilateral model as the bilateral injection of this compound into the striatum produces not only severe adipsia, aphagia and seizures but also death more often than not. Turning behavior to amphetamine or apomorphine following unilateral application of 6-OHDA gauges the extent of the induced SNpc or striatal lesion and this behavior has been used to test the efficacy of potential PD therapeutics. What makes 6-OHDA an attractive candidate as a possible endogenous toxin inhe initiation of the PD neurodegenerative process is the fact that it is a product of endogenous dopamine metabolism[17] and, as a neurotoxin it does produce lesions in the nigrostriatal DA pathway. it has been measured in the brains of levodopa-treated rats subjected to MPTP treatment, 6-

OHDA has yet to be recovered from the PD brain [personal communication. Ungerstedt U. 6-Hydroxy-dopamine induced degeneration of central mono- amine neurons. Eur J Pharmacol 1968; 5: 107–10.

MPTP Model

MPTP was the accidental tourist in a synthesis process gone awry and, although it may have caused some mayhem in certain circles, it was indeed a godsend to PD researchers. Oxidative stress, reactive oxygen species, energy failure, and inflammation have consistently been pointed to as hallmarks of PD. And, MPTP, as the gold standard model of PD, has repeatedly demonstrated this ranking among PD researchers by replicating almost all of the hallmarks of PD in monkeys[18] and other higher mammals and a significant number of these hallmarks in mice, but not in rats, which were found to be resistant to this toxin.[19] Lacking here is the definitive hallmark of PD, the Lewy body. But even this may become a reality with MPTP depending on how it is administered. Once in the brain, MPTP is taken up by the astrocytes, and is metabolized to MPP+, its active metabolite, by monoamine oxidase-B (MAO-B). Recent findings show that once released from the astrocytes into the extracellular space via the OCT-3 transporter.[20], MPP+ is taken up into the neuron by the dopamine transporter and can be stored in vesicles via uptake by the vesicular monoamine transporter. It can block the complex I site and initiate other intercellular reactions. Since the storage vesicles have a limited capacity, MPP+ most likely pushes DA out into the intercellular space where it can be metabolized to a number of compounds some of which are toxic, like DOPAL[21] and where it can be subjected to superoxide radical (5-cysteinyl-DA) and hydroxyl radical attack (6-OHDA). Many studies have added Lewy-like bodies to the list of demonstrated hallmarks and although this hallmark has yet to be proven with certainty in mammals other than primates, these studies tell us that, given the right circumstances, we may be able to produce all of the hallmarks of PD. Of course, this would necessitate playing with different dosing and timing schedules and verifying what we find. And, along this line, MPTP-induced behavior warrants investigation to complete the model as there is a behavioral component to Parkinson disease.

The pesticide/herbicide models

Paraquat

MPP+ was developed in the 1950s under the name of cyperquat for possible pesticide use. Fortunately for us, this compound never reached the market and faded into pesticide

obscurity. Epidemiological reports suggest that pesticide use increases the risk of developing PD, but in the case of paraquat, this may be highly speculative as there have been only 95 cases of PD linked to paraquat toxicity.[22] Paraquat (N,-N-dimethyl- 4–4–4-bipiridinium) is used widely in agriculture. It is an herbicide (weed killer) that exhibits a structural resemblance to MPP+ and because of this structural similarity, it was reasoned that paraquat should behave like MPP+. However, unlike MPP+, paraquat exerts its deleterious effects through an oxidative stress mediated by redox cycling, which generates reactive oxygen species, particularly the superoxide radical, hydrogen peroxide and the hydroxyl radical that lead to the damage of lipids, proteins, DNA and RNA. Recent evidence on the effects of paraquat in the nigrostriatal DA system is somewhat confusing in that, on the one hand, reports note that, following the systemic application of this herbicide to mice, the animals exhibit reduced motor activity and a dose-dependent loss of striatal TH-positive striatal fibres and SNpc neurons. However, in contrast to the afore-mentioned findings, other researchers claimed that they found no paraquat-induced changes in the nigrostriatal DA system.[23] Paraquat is importances to PD researchers are its induced increase in synuclein in individual DA neurons in the SNpc and its induced presence of Lewy-like bodies in the DA neurons of the SNpc. The place of paraquat in PD research is that it may allow us to study the process of Lewy body formation in DA neurons as well as the role of synuclein in PD, should the above observations be confirmed. Furthermore, with only 95 absolute PD cases to attest to, can we really consider this herbicide as a risk factor for the development of Parkinson disease.

Rotenone

Paraquat and rotenone are pure herbicide and an insecticide. Its half-life is 3–5 days depending on exposure to sunlight. Like MPTP, it is highly lipophilic and readily crosses the blood–brain barrier. Rotenone seems to replicate almost all of the hallmarks of PD, including complex I blockade, behavioral alterations, inflammation, synuclein aggregation, Lewy-like body formation, oxidative stress and gastrointestinal problems.[24] The apparent beauty of this model is that, like paraquat, it was reported to cause synuclein aggregation and Lewy-like body formation. The difficulty about the use of rotenone as a model of Parkinson Disease is that although it does augment DA oxidation, evidence is slim on depletion of DA in the nigrostriatal system. Furthermore, thus far, there are no documented cases of rotenone-induced Parkinson Disease in humans.

Reserpine Model

Reserpine is the antihypertensive agent, induces depletion of central catecholamines stores. Injection of reserpine causes hypokinesia, rigidity, tremors, and immobility in rats. The animals were treated with reserpine (5 mg/kg, i.p., for 5 consecutive days). After 24 h of last treatment animals were tested for induction of severity of tremors by giving the scores as follows: No tremors-0, occasional twitches-1, moderate or intermittent twitches-2, continues tremors-3. The number of tremors was counted for 5 min. If animals were not showing tremors then 0 score was given, if animals showed 1 or 2 tremors then 1 score was given, animals showed 3 or 5 tremors in 5 min then 2 score was given and for 6 or more tremors, score was given 3. Akinesia was determined by holding the tail of animal and putting the front paws on the platform and let the animal to walk while holding (number of steps taken with forelimbs of animal were counted for 3 min) and muscular rigidity was determined by suspending the animal with forelimbs on middle part of horizontal glass rod (0.5 cm diameter) at the height of 25 cm above the table top and time to fall on the bottom surface was measured. The cut-off was kept for 1 min. The animals were treated with MEBV (100, 200 and 300 mg/kg, p.o., respectively), or L-dopa-carbidopa (30 mg/kg p.o.) 60 min before administration of reserpine for 5 consecutive days.[25]

Japanese encephalitis virus induced Parkinson's disease

In Fischer rats infected with Japanese encephalitis virus at 13 days after birth and sacrificed 12 weeks later, the major pathological changes resembled those found in Parkinson's disease. Specifically there was neuronal loss with gliosis which was confined mainly to the zona compacta of the substantia nigra, with a notable absence of lesions in the cerebral cortex and cerebellum. Changes were bilateral being most severe in the central part of the zona compacta. Immunohistochemical studies with anti-tyrosine hydroxylase demonstrated that the number of TH-positive neurons was significantly decreased in the substantia nigra compared to controls, while comparable numbers of tyrosine hydroxylase-positive neurons were found in the basal ganglia in both JEV- treated rats and age-matched controls. JEV-infected rats showed marked bradykinesia, with significant behavioral improvement being observed following administration of L-DOPA. Immunohistochemical studies failed to detect JEV antigens in any region of the rat brain and the JEV genome was undetectable in the substantia nigra and the cerebral cortex using the reverse transcription-polymerase chain reaction (RT±PCR). The findings suggest that JEV infection of rats under the conditions described may serve as a model of virus induced Parkinson's Disease. Albino rats of the

Fischer strain were obtained from SLC Japan. The virus strain used was the JaGAr-01 strain of JEV. Supernatants from 10% homogenates of infected mouse brains (109 PFU/ml) were diluted with 20% Hemacel (Hoechst) in Eagle's minimum essential medium and stored at 7708C until use. Virus (0.03 ml containing 36106 PFU) was inocu- lated intracerebrally with a specially designed two- step thin 27 gauge needle (Hoshimori Iryoki KK, Tokyo, Japan) with a stopper 3 mm from the tip. The site of inoculation was located at the midpoint of the line connecting the left eye to the midpoint between the right and left ears. Hemacel (20%) in Eagle's minimum essential medium was injected into control rats.[26]

Classification of antiparkinsonian drugs

- **1) Drugs affecting brain dopamine systems**
- Dopamine precursor: Levodopa (DA does not cross BBB)
- Peripheral decarboxylase inhibitors: Carbidopa, Benserazide.
- Dopaminergic agonist: Bromocriptine, Pergolide, Piribedi, Ropinirole, Pramipexole.
- MAO-B inhibitors: Seligiline.
- COMT inhibitors: Entacopone, Tolcapone.
- Dopamine facilator: Amantadine.

- **2) Drugs affecting brain cholinergic system**
- Central anticholinergics: Trihexyphenidyl, Procyclidine, Biperiden.
- Antihistaminics: Ophenadrine, Promethazine.[27]

Sinemet (Levodopa/Carbidopa)

Levodopa (also called L-dopa) is the most commonly prescribed and most effective drug for controlling the symptoms of Parkinson's disease, Levodopa is transported to the nerve cells in the brain that produce dopamine. It is then converted into dopamine for the nerve cells to use as a neurotransmitter. Sinemet is made up of levodopa and another drug called carbidopa. Levodopa enters the brain and is converted to dopamine while carbidopa increases its effectiveness and prevents or lessens many of the side effects of levodopa, such as nausea, vomiting, and occasional heart rhythm disturbances. It is generally recommended that patients take Sinemet on an empty stomach, at least 30 minutes before, or one hour after meals. There are two forms of Sinemet, controlled-release or immediate-release Sinemet. Controlled-release (CR) Sinemet and immediate-release Sinemet are equally effective in treating the symptoms of Parkinson's disease, but some people prefer the controlled release version. Ask your doctor which approach is best for

you. While Sinemet is the most effective medication and has the least short-term side effects, it is associated with risks of long-term side effects, such as involuntary movements dyskinesia.

Levodopa may also cause restlessness, confusion, or abnormal movements. Changes in the amount or timing of the dose will usually prevent these side effects, but most experts now recommend starting with alternatives to Sinemet, such as the dopamine agonists, and use Sinemet when the alternatives fail to provide sufficient relief.[28]

Dopamine Agonists

Dopamine agonists are drugs that activate the dopamine receptor. They mimic or copy the function of dopamine in the brain. Requip (ropinirole), Mirapex (pramipexole), and Neupro (rotigotine) are dopamine agonists. These medications may be taken alone or in combination with Sinemet. Generally, dopamine agonists are prescribed first and levodopa is added if the patient's symptoms cannot be controlled sufficiently. Because dopamine agonists are better tolerated and do not have the same risks of long-term complications as levodopa therapy, dopamine agonists are often the first choice of treatment for Parkinson's disease. However, dopamine agonists do carry a risk of short-term side effects such as nausea, vomiting, dizziness, light-headedness, confusion, and hallucinations.

Symmetrel

Symmetrel (Amantadine) may be a helpful treatment for people with mild Parkinson's disease, but it may cause side effects including confusion and memory problems. Symmetrel increases the amount of dopamine available for use in the brain, therefore reducing symptoms of Parkinson's. There have been recent reports that Symmetrel may help reduce the involuntary movements (dyskinesia) associated with levodopa therapy.

Anticholinergics (Artane, Cogentin)

Anticholinergics are used to restore the balance between the two brain chemicals, dopamine and acetylcholine, by reducing the amount of acetylcholine. This acts to reduce tremor and muscle stiffness in people with Parkinson's. These medications, however, can impair memory and thinking, especially in older people; therefore, they are rarely used today.[29]

Eldepryl Seligiline

This drug used with or without carbidopa- levodopa therapy, helps prevent the breakdown of both naturally occurring dopamine and dopamine formed from levodopa. It does this by

inhibiting the activity of the enzyme monoamino oxidase–B (MAO-B), the enzyme that metabolizes dopamine in the brain. Research has shown that seligiline may delay the need for carbidopa-levodopa about a year, and when taken with carbidopa-levodopa may enhance the drug's effectiveness. At one time it was though that this drug might slow the progression of Parkinson's disease, but this now appears not to be the case Common side effects include nausea, dizziness/fainting, and stomach pain.[30]

Tasmar, Comtan (COMT Inhibitors)

When COMT is blocked, dopamine can be retained and used more effectively, reducing Parkinson's symptoms. COMT inhibitors like Tasmar(tolcapone) and Comtan (entacapone) can also increase the effectiveness of levodopa.

CONCLUSION

Parkinson Disease is a disorder of the central nervous system, involving primarily a degeneration of certain nerve cells in deep parts of the brain called the basal ganglia, and in particular a loss of nerve cells (or neurons) in a part of the brainstem called the substantia nigra. Parkinson disease is a chronic, progressive, neurodegenerative disorder with an estimated prevalene of 31 to 328 per 100,00 people worldwide. Deep Brain Stimulation for Parkinson's disease was developed based on findings from ablative surgical procedures. Researchinto its use decreased with the advent of levodopa butresumed in the early 1990s due to frequent motor complications and symptoms refractory to dopaminergic therapy. extensive education of thehealthcare community, especially neurologists, is crucial inorder to provide the intervention for appropriately selected candidates.

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