

Parkinson's Disease and Its Treatment

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Goals and Objectives

Goals:

To provide the pharmacist with information about Parkinson's disease and its treatment

Objectives:

After reading this continuing education article, the pharmacist should be able to do the following:

1. Discuss the various etiologies of Parkinson's disease.
2. Describe the major signs and symptoms associated with the disease.
3. Outline a rational therapeutic approach for the treatment of Parkinson's disease.
4. Name the principal drugs and chemicals that may cause symptoms of the ailment.
5. List the major advantages and disadvantages of the drugs used to treat Parkinson's disease.
6. Counsel patients regarding the appropriate administration, adverse effects, and drug interactions associated with the drugs used in the treatment of Parkinson's disease.

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Universal Program Number 406-000-06-006-H01.

The expiration date for this program is 5/31/09.



In 1817, Dr. James Parkinson, a London practitioner, first described a disease he called “shaking palsy” in a monograph entitled “An Essay on Shaking Palsy.” Although his description has been refined, it has not been modified appreciably and remains the basis for the signs of Parkinson’s disease.

Parkinson’s disease is a progressive neurological disorder marked by tremor, rigidity, muscular weakness, and a peculiar gait. Although this modern description is very similar to Dr. Parkinson’s terminology, the exact etiology of this disease remains unknown.

Incidence of Parkinson’s Disease

The risk of developing Parkinson’s disease during one’s lifetime is 2% to 3%. About 1% of the nation’s population over age 50 is affected with the disease, and each year there are an additional 20 new cases per 100,000 population. Men and women appear to be equally subject to Parkinson’s disease. The disease is encountered in all races throughout the world. More than 65% of those afflicted have an onset of symptoms between 50 and 69 years of age. The average age of onset is 60 years and onset under the age of 40 is uncommon.

Etiology of The Disease

The typical signs and symptoms of Parkinson’s disease can be demonstrated in many conditions; therefore, before its diagnosis can be established, other causes of these signs and symptoms must be examined. The major possibilities include idiopathic parkinsonism, chemical and drug-induced Parkinson’s disease and other types of secondary parkinsonism.

The term “idiopathic” indicates an unknown cause. Many theories have been postulated, but lack of supporting evidence regarding suspected causes, such as head injuries, viruses, and allergic reactions, has resulted in the etiology of this disease remaining unknown.

Numerous chemicals and drugs may cause symptoms resembling Parkinson’s disease, when large amounts are acutely ingested or when people are subjected to chronic exposure (Table 1). Chronic exposure to certain heavy metals, such as lead or mercury, may result in symptoms similar to Parkinson’s disease. Certain photographic dyes, carbon monoxide, carbon disulfide, cyanide, and methyl chloride have produced some of the signs associated with this disease. Iatrogenic Parkinson’s disease occurs with a variety of drugs (Table 1), but is most commonly associated with the phenothiazine tranquilizers. These drugs produce extrapyramidal side effects which ultimately may produce a parkinson-like disorder.

Other drugs with central nervous system activity, including reserpine, carbamazepine, have been implicated in causing extrapyramidal adverse effects with manifestations similar to Parkinson’s disease.

Historically, both postencephalic (i.e., encephalitis lethargica) and infectious (i.e., syphilis, malaria, poliomyelitis) etiologies have been investigated. Other uncommon causes have included trauma, such as injuries to the head, and tumors, primarily intracranial tumors. Juvenile parkinsonism is extremely rare, and is associated primarily with Wilson’s disease, a hereditary disorder of copper metabolism in which abnormal amounts of copper are deposited in certain organs, such as the brain. Atherosclerosis may also produce some of the symptoms; in these cases, however, the symptoms vary, and are not consistent with typical Parkinson’s disease.

Although the exact cause of Parkinson’s disease is unknown, there have been a variety of theories postulated. The primary signs (rigidity, resting tremor, bradykinesia) reflect loss of cells within the midbrain nucleus, the substantia nigra, which is associated with neurons that release dopamine. Consequently, the loss of cells in this area will result in symptoms associated with reduced performance of dopamine. Another theory proposes that the degradation of dopamine by monoamine oxidase (MAO) results in oxidation processes. This oxidative stress is damaging to the substantia nigra because of high concentrations of dopamine in the area. Another biochemical theory indicates that there appears to be both a cholinergic component and a dopamine deficiency. The former is exhibited as a predominantly excitatory effect on the central nervous system (CNS); however, the major problem appears to be a dopamine deficiency. Normally, there is a balance between the excitatory cholinergic effects produced by acetylcholine and the inhibitory effects associated with dopamine. However, the dopamine deficiency results in an excess of acetylcholine effects, while the concentration of acetylcholine remains unchanged. Although these alterations are a problem, other neurotransmitters are also in the brain (e.g., serotonin) and may have some role in Parkinson’s disease.

Clinical Findings

The diagnosis of parkinson’s disease is difficult during the early stages of the disease because it has a gradual onset with vague complaints and symptoms. However, when the classic tremor appears, the diagnosis is easily made.

The symptoms of advanced Parkinson’s disease are unique. The classical symptoms include rigidity, bradykinesia, seborrhea, festination gait, flexed posture, salivation, and a “pill-rolling” hand tremor. The patient often maintains a catatonic-like position, with a fixed stare. These multiple features are encompassed in three general categories: bradykinesia, rigidity, and tremor.

Bradykinesia and akinesia are a slowing down of voluntary actions with obvious difficulty in initiating movement. This may be severe, and results in an immobility. These symptoms can be evaluated by requiring a patient to perform rapid alternating movements.

The rigidity is an abnormal plasticity of muscles which causes resistance to movement. Consequently, the patient cannot coordinate fine movements, and usually makes gross movements. While walking, the patient may begin to trot (festination gait) because of the rigidity. Muscle control and normal associated movements are hampered.

The tremor is usually present at rest, and briefly disappears during purposeful movement, i.e., reaching for an object. The patient exhibits a “pill-rolling” tremor by movement of the thumb over the middle and index fingers. The tremor may cause a loss of dexterity, and such simple tasks as buttoning clothing, tying shoes, and writing may become difficult. Autonomic nervous system abnormalities (i.e., constipation, perspiration, salivation) and referred pain sensations are common symptoms. The complex nature and insidious onset and typical progression of Parkinson’s disease has resulted in a mechanism for staging with regard to the severity of Parkinson’s disease (Table 2).

General Treatment

In some patients, physical therapy is useful for reducing akinesia and bradykinesia. However, purely neurological symptoms, such as tremor and rigidity, do not respond to physical therapy. Exercise and massage are also employed in the therapy to relieve and reduce symptoms.

Parkinson’s disease can be aggravated by psychological factors. The patient can become defensive, hostile, and/or introverted by the appearance of obvious symptoms; therefore, it is important that understanding and reassurance by family members and by health care personnel be a part of the general treatment.

Both physical and psychological therapy, such as short walks and recreational outings, should be encouraged in order to maintain the patient’s motivation and general well-being.

Drug Therapy

Levodopa is the drug of choice for Parkinson’s disease patients who are symptomatic and have sufficient locomotor impairment to limit their productivity. Anticholinergic agents, bromocriptine, and other drugs may also be used and will be discussed. Although its exact mechanism of action is unclear, levodopa, an immediate precursor of dopamine, easily crosses the blood brain barrier and is converted to dopamine in the basal ganglia. Because a current theory states that Parkinson’s disease is caused by the lack of dopamine in the basal ganglia, levodopa is used to supply the dopamine needed to overcome the symptoms. Dopamine itself does not cross the blood brain barrier.

Levodopa produces 50%, or greater, improvement in more than 60% of treated patients. Typically, akinesia is the initial symptom to improve followed by an improvement in rigidity and tremor. The usual effective dose of levodopa varies from 2 Gm to the maximum of 8 Gm daily, in divided doses, administered with meals or food. Therapy is initiated with doses of 200 mg to 500 mg, and increased every three to four days by several hundred milligrams until full dosage is achieved.

Because a large amount of levodopa is metabolized peripherally before it reaches the brain, concurrent administration of a decarboxylase inhibitor, such as carbidopa prevents the peripheral metabolism and allows for a 80% reduction in the dose of levodopa. The dose of levodopa should not exceed to two grams daily when combined with carbidopa.

There are several other drugs used to extend the effects of levodopa. These include tolcapone and entacapone. Entacapone is a catechol-O- methyltransferase (COMT) that is used with levodopa/carbidopa in patients with Parkinson’s disease to prevent the end-of-dose “on-off” symptoms. Levodopa is metabolized in part by COMT. As entacapone inhibits peripheral COMT, plasma concentrations of levodopa are increased. Entacapone reaches peak serum concentrations in about one hour after oral administration, is metabolized in the liver, eliminated primarily in the bile, and has a half-life of less than two hours. Side effects associated with the use of entacapone include levodopa-related effects (e.g., anorexia, insomnia, nausea), orange discoloration of urine and potential interactions with drugs that are metabolized by COMT (e.g., isoproterenol, dopamine, epinephrine). The usual dosage for entacapone is 200 mg with each levodopa-carbidopa dose, up to a maximum of 8 doses per day. Tolcapone has a longer half-life than entacapone and is used in a dose of 100 mg three times a day. However, there have been several incidences of severe hepatotoxicity. If tolcapone is used, hepatic function must be carefully monitored. In addition, gastrointestinal adverse effects (e.g., diarrhea) may be an issue.

When administered orally, approximately 80% of a levodopa dose is absorbed. Levodopa, which can be used in a maximum daily dose of 8 grams, reaches peak levels within two hours, is metabolized rapidly, and the metabolites are eliminated in the urine within six hours.

A major problem with levodopa is that most patients experience multiple side effects, which are usually dose-dependent and reversible. Nausea, vomiting, and anorexia occur frequently in patients receiving this agent. Involuntary movements occur in approximately half of the patients on chronic levodopa therapy. These include gnawing, chewing, twisting and grimacing.

Many of the problems associated with levodopa therapy are related to the progressive nature of Parkinson’s disease. As fewer and fewer terminals are available to process exogenously administered levodopa and converting it to dopamine, there is less dopamine being formed to be used. Therefore, the effects of levodopa are reduced and the “on-off” phenomenon associated with levodopa occurs. In this situation, there appears to be a sudden loss of efficacy. This “on-off” activity may be impeded by more frequent administration of levodopa and does not respond well to simply increasing the dose of levodopa.

Levodopa produces many CNS and psychiatric disturbances which vary in intensity from mild to severe. A variety of cardiovascular adverse effects are also associated with levodopa therapy.

Numerous other side effects and cautions, including respiratory, renal and ophthalmic adverse effects, are associated with levodopa therapy.

A variety of drug interactions have likewise been associated with levodopa. For example, monoamine oxidase inhibitors should not be administered during levodopa therapy because hypertensive crisis may result. In addition, pyridoxine hydrochloride (vitamin B-6) in doses greater than 5 mg causes a reversal of the effects of levodopa except when it is combined with carbidopa. Levodopa should be used with caution in patients receiving methyl dopa or guanethidine, because the hypotensive effect of levodopa may necessitate dosage reduction of those drugs. Phenothiazines and butyrophenones, as well as other antipsychotic agents, antagonize the therapeutic effect of levodopa, and should be used with caution or not at all during levodopa therapy. Similar effects have been encountered with benzodiazepines, papaverine, and phenytoin.

Although levodopa may not be a panacea, it is a major therapeutic agent. It not only has provided a unique mechanism for treating Parkinson's disease, but it has also created a new area of research for developing treatment modalities for a disease that had been treated by the same method for a century.

The anticholinergic agents were the treatment of choice for Parkinson's disease for many years. The efficacy of these drugs appears to be related to their central cholinergic blocking action. The drugs frequently used include trihexyphenidyl and benztropine. Trihexyphenidyl differs chemically from benztropine. In addition, several antihistamines (i.e., diphenhydramine) are useful in some Parkinson's disease patients because of the agents' anticholinergic effects.

Many times the adverse effects of these drugs, such as constipation, psychic disturbances, urinary retention, and tachycardia, occur before the desired dose can be achieved. Although the anticholinergics are not drugs of choice in the treatment of Parkinson's disease, they are still useful in some mild cases either combined with levodopa or given singly to those patients who can't tolerate levodopa. The anticholinergics seldom produce better than a 20% improvement in symptoms which may continue to progress despite treatment.

Amantadine is an antiviral drug that is used in the prevention and symptomatic treatment of influenza caused by certain influenza A virus strains. It is also a useful drug in treating idiopathic parkinsonism.

The mechanism of action of amantadine in Parkinson's disease is unknown, but does not appear to be associated with its antiviral effects. Amantadine does not exhibit significant anticholinergic activity, but appears to have CNS dopaminergic activity as well as the ability to block the re-uptake of dopamine into presynaptic neurons. Each of the catecholaminergic activities produces an increase in available dopamine within the CNS.

Amantadine is well absorbed from the gastrointestinal tract, and produces steady state blood levels within several days. Amantadine is excreted unchanged in the urine with an average elimination half-life of 24 hours. Acidification of the urine increases the rate of excretion, while the half-life of amantadine is prolonged in patients with renal dysfunction.

Like levodopa, amantadine does not alter the course of Parkinson's disease. It is not as effective as levodopa, but appears to be at least as effective as the anticholinergic drugs in treating Parkinson's disease. In addition, it is very effective in treating iatrogenic extrapyramidal symptoms, and is particularly useful when anticholinergic drugs are contraindicated. Combinations of amantadine with other drugs used in Parkinson's disease, particularly levodopa, are often more effective than either drug alone. This is especially beneficial to those patients who cannot tolerate large doses of levodopa and, also, during initial phases of levodopa therapy, because objective improvement occurs rapidly with amantadine and very slowly with levodopa. The usual oral dose of amantadine in treating Parkinson's disease is 100 mg twice daily, while a maximum of 400 mg daily may be administered.

Although amantadine does not exhibit as many side effects as levodopa, it does possess a variety of undesirable properties. Many of these are displayed as psychic or CNS abnormalities which are reversible, frequently dose-related, and may appear within a few hours or days after initiation of amantadine therapy or following an increase in drug dosage. These side effects include fatigue, mental depression, anxiety, insomnia, confusion, headache, visual hallucinations, and nervousness. Livedo reticularis, a reddish-blue netlike mottling of the skin, is an adverse effect in patients receiving amantadine for Parkinson's disease.

Bromocriptine is a direct-acting dopamine agonist. Unlike levodopa, bromocriptine does not require conversion to an active form to be effective. As Parkinson's disease progresses, the brain appears to lose its ability to convert levodopa to dopamine; therefore, the patient may become refractory to the beneficial effects of levodopa. Bromocriptine appears to be quite effective, and is usually reserved for those patients who have advanced disease and who no longer respond to levodopa alone. Bromocriptine works rapidly and is well absorbed from the gastrointestinal tract with peak plasma levels and maximal clinical response occurring approximately 100 minutes after an oral dose. Bromocriptine has a half-life of 6 to 8 hours, and is extensively metabolized and eliminated primarily by biliary pathways. The maintenance dose is individualized and is administered with food. The adverse effects associated with bromocriptine are similar to those of levodopa. There appears to be a decreased occurrence of the "on-off" effect and involuntary abnormal movements, but mental changes and orthostatic hypotension occur more frequently with bromocriptine.

Selegiline is a selective type B monoamine oxidase inhibitor (inhibits the catalytic breakdown of dopamine in the brain). Therefore, selegiline is the drug that should be used provided Parkinson's disease occurs as a result of oxidative stress from the breakdown of monoamines (particularly dopamine) in the brain. Selegiline would provide a protective barrier to this effect.

Selegiline is rapidly absorbed from the gastrointestinal tract, readily crosses the blood brain barrier, and is relatively long acting. Selegiline has exhibited few serious adverse effects. Gastrointestinal and central nervous system effects have been encountered. The usual dose for selegiline is 5 to 10 milligrams daily and it can be used in combination with levodopa.

Pergolide is an ergoline derivative that directly stimulates postsynaptic dopamine receptors. It is used with levodopa-carbidopa in patients with complex Parkinson's disease. Pergolide directly stimulates specific dopamine receptors and is more potent and longer acting than bromocriptine.

Pergolide is rapidly absorbed, detected in plasma within 30 minutes and achieves peak plasma levels in three hours. Pergolide has a half-life of from 18 to 40 hours after administration. Pergolide is extensively bound to plasma proteins and is metabolized to a variety of substances, some of which have dopamine receptor agonism. Adverse effects associated with pergolide include nausea, diarrhea, constipation, dizziness, hallucinations, and respiratory and cardiovascular effects. Pergolide is implicated in a high frequency of adverse effects.

Ropinirole is a dopamine agonist that is used for treating early (without levodopa) and advanced (with levodopa) Parkinson's disease. Ropinirole is a dipropylaminoethyl-indole compound that stimulates specific dopamine receptors in the brain. Ropinirole is well absorbed after oral administration and achieves peak serum concentrations in about two hours. Ropinirole is metabolized in the liver to inactive metabolites, eliminated in the urine, and has a half-life of about six hours. Adverse effects associated with the use of ropinirole include syncope, bradycardia, nausea and somnolence. The usual dose of ropinirole varies from patient to patient with a maximum dose of 24 mg a day.

Pramipexole is a dopamine agonist that is used for treating early (without levodopa) and advanced (with levodopa) Parkinson's disease. Pramipexole is a propylaminobenzothiazole compound that stimulates specific dopamine receptors in the brain. Pramipexole is well absorbed from the gastrointestinal tract with serum concentrations reaching a peak within two or three hours. Pramipexole is eliminated unchanged in the urine with a half-life of 8 to 12 hours. Renal impairment can reduce the elimination of pramipexole. Adverse effects associated with the use of pramipexole include hallucinations, nausea, somnolence, and rarely, orthostatic hypotension. The usual dose of pramipexole varies from patient to patient with a maximum dose of 4.5 mg a day.

Monitoring By The Pharmacist

Parkinson's disease is an insidious, progressive disorder. Drugs, especially levodopa, often relieve many of the major symptoms, but do not cure the disease. Since the introduction of levodopa, the mortality rate of individuals with Parkinson's disease is approaching that of the general population.

Treatment success is dependent on continued encouragement and appropriate monitoring and counseling. The patient with Parkinson's disease is an ideal candidate for outpatient monitoring by the pharmacist because the diagnosis is known; the drugs used are for long-term effects, and may cause multiple adverse effects; and a variety of other therapeutic components of treatment often require counseling by health professionals. The knowledgeable and sympathetic pharmacist should be able to significantly contribute to the success of the therapeutic program for these patients.

Bibliography

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Table 1
Examples of Chemicals and Drugs
Which May Cause Parkinson-Like Effects

amitriptyline	methyl chloride
carbamazepine	methyldopa
carbon monoxide	Photographic dyes
cyanide	reserpine
lead	butyrophenones (e.g., haloperidol)
mercury MPTP	phenothiazines (e.g., trifluoperazine)

Table 2
Stages of Parkinson's Disease

Stage	Description
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0	No clinical signs evident
I	Unilateral involvement
II	Bilateral involvement but no postural abnormalities
III	Bilateral involvement with mild postural imbalance on examination or history of poor balance or falls; patient leads independent life
IV	Bilateral involvement with postural instability; patient requires substantial help
V	Severe, fully developed disease; patient restricted to bed or wheelchair

Table 3
TYPICAL DRUGS USED TO TREAT PARKINSON'S DISEASE

Generic Name	Example of Brand Name
Amantadine	Symmetrel
Benzotropine	Cogentin
Bromocriptine	Parlodel
Diphenhydramine	Benadryl
Entacapone	Comtan
Levodopa	Larodopa
levodopa & carbidopa	Sinemet
Pergolide	Permax
Pramipexole	Mirapex
Ropinirole	Requip
Selegiline	Eldepryl
Tolcapone	Tasmar
Trihexphenidyl	Artane