Pharmacologic Management of Parkinsonism

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Learning objectives:

Following the lesson presentation students will be able to:

1. Describe parkinson and its pathophysiology briefly.
2. Describe the indications, mechanism of action, side effects, drug interactions and contraindications of anti-parkinson drugs

PARKINSONISM

Parkinsonism is characterized by a combination of rigidity, bradykinesia, tremor, and postural instability that can occur for a variety of reasons but is usually idiopathic. Cognitive decline occurs in many patients as the disease advances. Other non-motor symptoms—which are receiving increasing attention—are affective disorders (anxiety or depression), personality changes, abnormalities of autonomic function (sphincter or sexual functions; choking; sweating abnormalities; and disturbances of blood pressure regulation), sleep disorders, and sensory complaints or pain. The disease is generally progressive, leading to increasing disability unless effective treatment is provided. The normally high concentration of dopamine in the basal ganglia of the brain is reduced in parkinsonism, and pharmacologic attempts to restore dopaminergic activity with levodopa and dopamine agonists alleviate many of the motor features of the disorder. An alternative but complementary approach has been to restore the normal balance of cholinergic and dopaminergic influences on the basal ganglia with antimuscarinic drugs. The pathophysiologic basis for these therapies is that in idiopathic parkinsonism, there is a loss of dopaminergic neurons in the substantia nigra that normally inhibit the output of GABAergic cells in the corpus striatum. Drugs that induce parkinsonian syndromes either are dopamine receptor antagonists or lead to the destruction of the dopaminergic MPTP.

1) LEVODOPA

Dopamine does not cross the blood-brain barrier and if given into the peripheral circulation has no therapeutic effect in parkinsonism. However, levodopa, the immediate metabolic precursor of dopamine, does enter the brain), where it is decarboxylated to dopamine. Unfortunately, only about 1–3% of administered levodopa actually enters the brain unaltered; the remainder is metabolized extracerebrally, predominantly by decarboxylation to dopamine, which does not

penetrate the blood-brain barrier. Accordingly, levodopa must be given in large amounts when used alone. However, when given in combination with a dopa decarboxylase inhibitor that does not penetrate the blood-brain barrier, the peripheral metabolism of levodopa is reduced, plasma levels of levodopa are higher, plasma half-life is longer, and more dopa is available for entry into the brain. Indeed, concomitant administration of a peripheral dopa decarboxylase inhibitor such as carbidopa may reduce the daily requirements of levodopa by approximately 75%. The best results of levodopa treatment are obtained in the first few years of treatment. This is sometimes because the daily dose of levodopa must be reduced over time to avoid adverse effects at doses that were well tolerated initially. Some patients become less responsive to levodopa, perhaps because of loss of dopaminergic nigrostriatal nerve terminals or some pathologic process directly involving striatal dopamine receptors. For such reasons, the benefits of levodopa treatment often begin to diminish after about 3 or 4 years of therapy, regardless of the initial therapeutic response. Although levodopa therapy does not stop the progression of parkinsonism, its early initiation lowers the mortality rate. However, long-term therapy may lead to a number of problems in management such as the on-off phenomenon. The most appropriate time to introduce levodopa therapy must therefore be determined individually. When levodopa is used, it is generally given in combination with carbidopa, a peripheral dopa decarboxylase inhibitor, which reduces peripheral conversion to dopamine. Combination treatment is started with a small dose, eg, carbidopa 25 mg, levodopa 100 mg three times daily, and gradually increased. It should be taken 30–60 minutes before meals. Levodopa can ameliorate many of the clinical motor features of parkinsonism, but it is particularly effective in relieving bradykinesia and any disabilities resulting from it. When it is first introduced, about one third of patients respond very

well and one third less well. Most of the remainder either are unable to tolerate the medication or simply do not respond at all, especially if they do not have classic Parkinson's disease.

Levodopa Adverse Effects:

A. Gastrointestinal Effects: When levodopa is given without a peripheral decarboxylase inhibitor, anorexia and nausea and vomiting occur in about 80% of patients. These adverse effects can be minimized by taking the drug in divided doses, with or immediately after meals, and by increasing the total daily dose very slowly. Antacids taken 30–60 minutes before levodopa may also be beneficial. Fortunately, tolerance to this emetic effect develops in many patients. Antiemetics such as phenothiazines should be avoided because they reduce the antiparkinsonism effects of levodopa and may exacerbate the disease. When levodopa is given in combination with carbidopa, adverse gastrointestinal effects are much less frequent and troublesome occurring in less than 20% of cases, so that patients can tolerate proportionately higher doses.

B. Cardiovascular Effects: A variety of cardiac arrhythmias have been described in patients receiving levodopa, including tachycardia, ventricular extrasystoles and, rarely, atrial fibrillation. This effect has been attributed to increased catecholamine formation peripherally. The incidence of such arrhythmias is low, even in the presence of established cardiac disease, and may be reduced still further if the levodopa is taken in combination with a peripheral decarboxylase inhibitor. Postural hypotension is common, but often asymptomatic, and tends to diminish with continuing treatment. Hypertension may also occur, especially in the presence of nonselective monoamine oxidase inhibitors or sympathomimetics or when massive doses of levodopa are being taken.

C. Behavioral Effects: A wide variety of adverse mental effects have been reported, including depression, anxiety, agitation, insomnia, somnolence, confusion, delusions, hallucinations, nightmares, euphoria, and other changes in mood or personality. Such adverse effects are more common in patients taking levodopa in combination with a decarboxylase inhibitor rather than levodopa alone, presumably because higher levels are reached in the brain. Several atypical antipsychotic agents that have low affinity for dopamine D2 receptors (clozapine, olanzapine, quetiapine, and risperidone) are now available and may be particularly helpful in counteracting such behavioral complications.

D. Dyskinesias and Response Fluctuations: Dyskinesias occur in up to 80% of patients receiving levodopa therapy for more than 10 years. In some patients, these fluctuations relate to the timing of levodopa intake (wearing-off reactions or end-of-dose akinesia). In other instances, fluctuations in clinical state are unrelated to the timing of doses (on-off phenomenon). In the on-off phenomenon, off-periods of marked akinesia alternate over the course of a few hours with on-periods of improved mobility but often marked dyskinesia. The phenomenon is most likely to occur in patients who responded well to treatment initially.

E. Miscellaneous Adverse Effects: Mydriasis and acute glaucoma

Drug Holidays: A drug holiday (discontinuance of the drug for 3–21 days) may temporarily improve responsiveness to levodopa and alleviate some of its adverse effects but is usually of little help in the management of the on-off phenomenon. Furthermore, a drug holiday carries the risks of aspiration pneumonia, venous thrombosis, pulmonary embolism, and depression resulting from the immobility accompanying severe parkinsonism. For these reasons and because of the temporary nature of any benefit, drug holidays are not recommended.

Drug Interactions

Pharmacologic doses of pyridoxine (vitamin B6) enhance the extracerebral metabolism of levodopa and may therefore prevent its therapeutic effect unless a peripheral decarboxylase inhibitor is also taken. Levodopa should not be given to patients taking monoamine oxidase A inhibitors or within 2 weeks of their discontinuance because such a combination can lead to hypertensive crises.

2. DOPAMINE RECEPTOR AGONISTS

Drugs acting directly on postsynaptic dopamine receptors may have a beneficial effect in addition to that of levodopa. Unlike levodopa, they do not require enzymatic conversion to an active metabolite, act directly on the postsynaptic dopamine receptors, have no potentially toxic metabolites, and do not compete with other substances for active transport into the blood and across the blood-brain barrier. Moreover, drugs selectively affecting certain (but not all) dopamine receptors may have more limited adverse effects than levodopa. A number of dopamine agonists have antiparkinsonism activity. The older dopamine agonists (bromocriptine and pergolide) are ergot (ergoline) derivatives, and are rarely—if ever—used to treat parkinsonism. Their side effects are of more concern than those of the newer agents (pramipexole and ropinirole).

There is no evidence that one agonist is superior to another; individual patients, however, may respond to one but not another of these agents. Dopamine agonists have an important role as first-line therapy for Parkinson's disease, and their use is associated with a lower incidence of the response fluctuations and dyskinesias that occur with long-term levodopa therapy. In consequence, dopaminergic therapy is often initiated with a dopamine agonist. Alternatively, a low dose of carbidopa plus levodopa is introduced, and a dopamine agonist is then added. In

either case, the dose of the dopamine agonist is built up gradually depending on response and tolerance. Dopamine agonists may also be given to patients with parkinsonism who are taking levodopa and who have end-of-dose akinesia or on-off phenomenon or are becoming resistant to treatment with levodopa. The response to a dopamine agonist is generally disappointing in patients who have never responded to levodopa.

Adverse effects: Anorexia, vomiting, Postural hypotension, Dyskinesia, Confusion, Hallucination, Psychosis

Ergot alkaloids adverse effects: Headache, nasal congestion, erythromelalgia, painless digital vasospasm

3. MONOAMINE OXIDASE INHIBITORS

Two types of monoamine oxidase have been distinguished in the nervous system. Monoamine oxidase A metabolizes norepinephrine, serotonin, and dopamine; monoamine oxidase B metabolizes dopamine selectively. Selegiline (deprenyl), a selective irreversible inhibitor of monoamine oxidase B at normal doses (at higher doses it inhibits monoamine oxidase A as well), retards the breakdown of dopamine; in consequence, it enhances and prolongs the antiparkinsonism effect of levodopa (thereby allowing the dose of levodopa to be reduced) and may reduce mild on-off or wearing-off phenomena. It is therefore used as adjunctive therapy for patients with a declining or fluctuating response to levodopa.

Rasagiline, another monoamine oxidase B inhibitor, is more potent than selegiline in preventing MPTP-induced parkinsonism the end points of the study.

Neither selegiline nor rasagiline should be taken by patients receiving meperidine, tramadol, methadone. The antitussive dextromethorphan should also be avoided by patients taking one of the monoamine oxidase B inhibitors; indeed, it is wise to advise patients to avoid all over-the-

counter cold preparations. Rasagiline or selegiline should be used with care in patients receiving tricyclic antidepressants or serotonin reuptake inhibitors because of the theoretical risk of acute toxic interactions of the serotonin syndrome type, but this is rarely encountered in practice. The adverse effects of levodopa may be increased by these drugs. The combined administration of levodopa and an inhibitor of both forms of monoamine oxidase (ie, a nonselective inhibitor) must be avoided, because it may lead to hypertensive crises, probably because of the peripheral accumulation of norepinephrine.

4. CATECHOL-O-METHYLTRANSFERASE INHIBITORS

Inhibition of dopa decarboxylase is associated with compensatory activation of other pathways of levodopa metabolism, especially catechol-O-methyltransferase (COMT), and this increases plasma levels of 3-O-methyldopa (3-OMD). Elevated levels of 3-OMD have been associated with a poor therapeutic response to levodopa, perhaps in part because 3-OMD competes with levodopa for an active carrier mechanism that governs its transport across the intestinal mucosa and the blood-brain barrier. Selective COMT inhibitors such as tolcapone and entacapone also prolong the action of levodopa by diminishing its peripheral metabolism. Levodopa clearance is decreased, and relative bioavailability of levodopa is thus increased. Neither the time to reach peak concentration nor the maximal concentration of levodopa is increased. These agents may be helpful in patients receiving levodopa who have developed response fluctuations. Tolcapone and entacapone are both widely available, but entacapone is generally preferred because it has not been associated with hepatotoxicity. The commercial preparation named Stalevo consists of a combination of levodopa with both carbidopa and entacapone.

5. APOMORPHINE

Subcutaneous injection of apomorphine, a potent nonergoline dopamine agonist that interacts with postsynaptic D2 receptors in the caudate nucleus and putamen, is effective for the temporary relief ("rescue") of off-periods of akinesia in patients on optimized dopaminergic therapy. It is rapidly taken up in the blood and then the brain, leading to clinical benefit that begins within about 10 minutes of injection and persists for up to 2 hours. Nausea is often troublesome, especially at the initiation of apomorphine treatment. Other adverse effects include dyskinesias, drowsiness, insomnia, chest pain, sweating, hypotension, syncope, constipation, diarrhea, mental or behavioral disturbances, panniculitis, and bruising at the injection site.

6. AMANTADINE

Amantadine, an antiviral agent, was by chance found to have relatively weak antiparkinsonism properties. Its mode of action in parkinsonism is unclear, but it may potentiate dopaminergic function by influencing the synthesis, release, or reuptake of dopamine. Amantadine is less efficacious than levodopa, and its benefits may be short-lived, often disappearing after only a few weeks of treatment. Nevertheless, during that time it may favorably influence the bradykinesia, rigidity, and tremor of parkinsonism. Adverse effects of amantadine include restlessness, depression, irritability, insomnia, agitation, excitement, hallucinations, confusion and livedo reticularis. Amantadine should be used with caution in patients with a history of seizures or heart failure.

7. ACETYLCHOLINE-BLOCKING DRUGS

A number of centrally acting antimuscarinic preparations are available that differ in their potency and in their efficacy in different patients. These agents may improve the tremor and rigidity of parkinsonism but have little effect on bradykinesia.

Reference:

Katzung BG and Trevor AG. Basic and Clinical Pharmacology, McGraw-Hill, 13th edition, 2015.

MCQ: Reason that dopamine itself is not used to treat in Parkinson's disease:

A) Dopamine is too expensive

B) The problem is cholinergic in nature, not dopamine

C) Dopamine does not cross the blood-brain barrier

D) Levodopa has a higher affinity for the D2 receptor