Drugs Used in Management of Parkinsonism

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Parkinsonism

- **Is characterized by a combination of rigidity, bradykinesia, tremor at rest, and postural instability.**
- **Cognitive decline may occur as the disease advances.**
- **Is generally a progressive incurable disorder.**
- **Associated with decreased dopamine concentration in the substantia nigra → …**

Parkinsonism

1. cholinergic predominance.
2. release of the inhibition of output of GABAergic cells in the corpus striatum.

- There is a loss of dopaminergic neurons in the substantia nigra which inhibit the output of GABAergic cells in the corpus striatum.
- Can be precipitated by dopamine receptor antagonists (antipsychotics).

Parkinsonism

- **MPTP (methylphenyl tetrahydropyridine) → destruction of nigrostriatal neurons.**
- **Neurotoxins and oxidation reactions generating free radicals may participate in pathogenesis of idiopathic parkinsonism.**
- **Genetic factors are involved in ~10-15% of cases.**

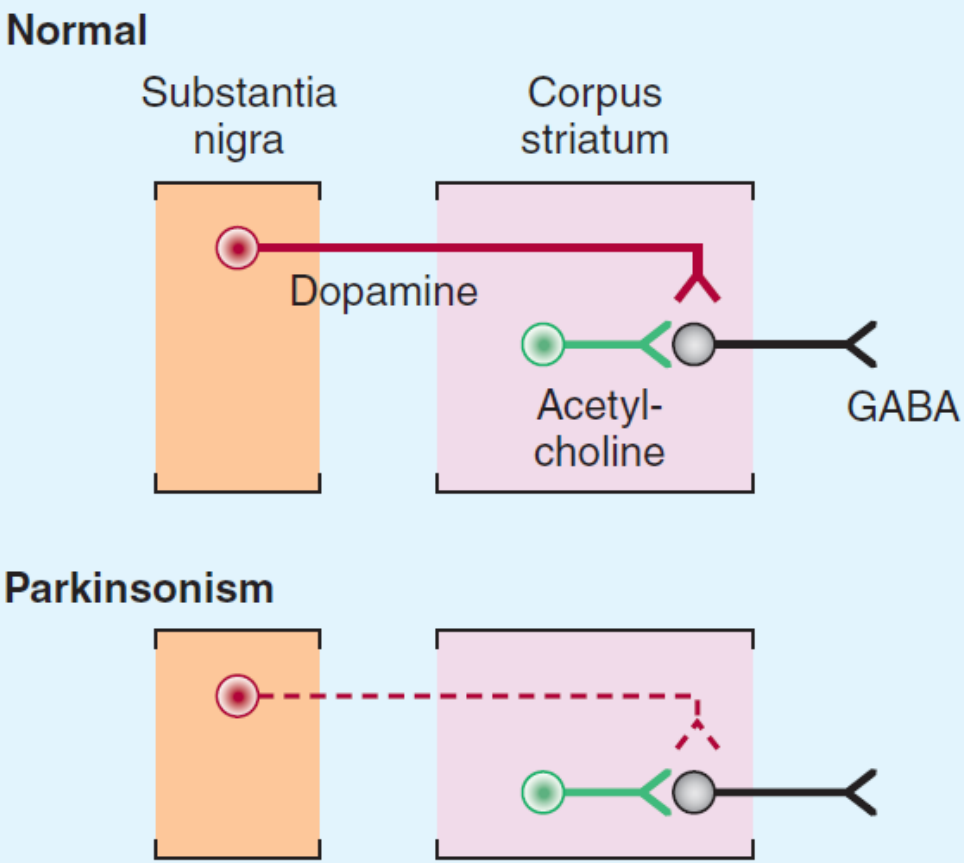

FIGURE 28–2:
Schematic representation of the sequence of neurons involved in parkinsonism.
Top: Dopaminergic neurons (red) originating in the substantia nigra normally inhibit the GABAergic output from the striatum, whereas cholinergic neurons (green) exert an excitatory effect.
Bottom: In parkinsonism, there is a selective loss of dopaminergic neurons (dashed, red).

Drugs for Parkinsonism

1. **Levodopa.**
2. **Dopamine receptor agonists: Bromocriptine, Pergolide, Pramipexole, Ropinirole.**
3. **Monoamine oxidase inhibitors: Selegiline, Rasagiline.**
4. **Catechol-O-methyltransferase inhibitors: Tolcapone, Entacapone.**

Drugs for Parkinsonism

5. **Amantadine.**
6. **Anticholinergic drugs: Benztropine, Biperiden, Orphenadrine, Procyclidine, Trihexyphenidyl.**

Levodopa

- **Dopamine has no therapeutic effect in parkinsonism if given systemically, because it does NOT cross the blood-brain-barrier.**
- **L-dopa, the immediate precursor of dopamine does enter the brain by the L-amino acid transporter, and is decarboxylated to dopamine.**

Levodopa

- **The benefits of dopaminergic antiparkinsonism drugs appear to depend mostly on stimulation of D_2 receptors, but D_1 receptor stimulation may also be required for maximal benefit.**
- **One of the newer drugs is D_3 selective.**

Levodopa

Pharmacokinetics:

- **Levodopa is rapidly absorbed from the intestine, but food delays its absorption.**
- **Certain amino acids from ingested food can compete with it for absorption and transport into the brain.**
- **Peaks in plasma 1-2 hours after the dose.**
- **Plasma t½ is ~ 1-3 hours.**

Levodopa

- It is metabolized in the periphery to homovanilic acid and dihydroxyphenyl acetic acid, and only 1-3% of the dose enters the brain.
- The rest is decarboxylated to dopamine in the periphery and does not enter the brain.
- Therefore, it should be given in large doses if used alone.
- 65% of the dose appear in urine within 8 hours of an oral dose.

Levodopa

- **The peripheral metabolism is reduced by giving a peripheral dopa decarboxylase inhibitor, carbidopa, which does not enter the brain → higher plasma levodopa levels (10% of dose enter the brain), and longer half-life.**
- **Carbidopa reduces levodopa dose by 75%.**

Levodopa

Therapeutic Use:

- **Levodopa can ameliorate all of the clinical features of parkinsonism, particularly the bradykinesia and the disabilities resulting from it.**
- **On administration, one third of patients respond well, and one third less well. The remainder are either not able to tolerate the medication or do not respond at all.**

Levodopa

- **Tolerance develops to levodopa, and responsiveness may be lost completely because of the disappearance of dopaminergic nigrostriatal nerve terminals or some pathologic process involving dopamine receptors.**
- **Usually the benefits begin to diminish after about 3-4 years of therapy.**

Levodopa

- **It does not stop the progression of parkinsonism, but it may reduce mortality rate.**
- **Levodopa is usually given in combination with carbidopa, which is available as 25/100 and 25/250 (carbidopa/levodopa).**
- **It should be taken 30–60 minutes before meals.**

Levodopa

Adverse Effects:

A. **Gastrointestinal effects:**

- **When given without carbidopa, ~ 80% of patients develop anorexia, nausea and vomiting. The vomiting is due to stimulation of the chemoreceptor trigger zone located in the brain stem but outside the blood brain barrier. Tolerance develops to vomiting.**
- **Domperidone may relieve persistent nausea.**
- **When given with carbidopa, less than 20% of patients experience this adverse effect.**

Levodopa

B. Cardiovascular effects:

1. **Cardiac arrhythmias including tachycardia, ventricular extrasystoles and atrial fibrillation due to increase catecholamine formation peripherally.**

- **Reduced when levodopa is given in combination with carbidopa.**

Levodopa

2. **Postural hypotension is common but often asymptomatic and tend to diminish with continuing treatment.**
3. **Hypertension occurs especially in the presence of nonselective MAOIs, sympathomimetics, and with massive levodopa doses.**

Levodopa

C. Dyskinesias:

- **Occur in 80% of patients of patients receiving levodopatherapy for more than 10 years.**
- **Vary between patients but tend to be constant in individual patients.**
- **It is dose-related.**
- **Choreoathetosis of the face and distal extremities is the most common.**

Levodopa

D. Behavioral effects:

- **Depression, anxiety, agitation, insomnia, somnolence, delusions, hallucinations, nightmares, euphoria, and other changes in mood or personality.**
- **These adverse effects are more common when levodopa is given in combination with carbidopa.**

Levodopa

E. Fluctuations in response:

1. **Related to timing of levodopa intake:**

   Wearing-off reactions or end-of-dose akinesia.

2. **Unrelated to timing of levodopa intake:**

- **“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 exact mechanism is unknown.**

Levodopa

F. Other adverse effects:

- **Mydriasis, which may precipitate an attack of acute glaucoma.**
- **Blood dyscrasias**
- **Positive Coombs test with evidence of hemolysis.**
- **Hot flushes.**
- **Aggravation or precipitation of gout.**

Levodopa

- **Abnormalities of smell and taste.**
- **Brownish discoloration of saliva, urine, or vaginal secretions.**
- **Priapism (nonsexual erection, pathologic).**
- **Mild and transient elevations of urea, liver enzymes and bilirubin.**

Levodopa

Drug Interactions:

1. Pyridoxine (vitamin B_6) enhances the extracerebral metabolism of levodopa and may interfere with its therapeutic effect unless carbidopa is also given.
2. Levodopa should not be taken with MAO-A inhibitors or within 2 weeks of their discontinuation, because hypertensive crisis may develop.

Levodopa

Contraindications:

1. **Psychotic patients (may exacerbate the mental disturbance).**
2. **Patients with angle-closure glaucoma.**
3. **Cardiac arrhythmias.**
4. **Peptic ulcer disease.**
5. **May activate malignant melanoma (levodopa is a precursor of skin melanin).**

Dopamine Receptor Agonists

- **Drugs acting directly on postsynaptic dopamine receptors:**

1. **Older drugs (ergot derivatives): Bromocriptine and pergolide.**
2. **Newer agents: Pramipexole and ropinirole.**

Dopamine Receptor Agonists

- **Unlike levodopa, they do not require enzymatic conversion to an active metabolite, act directly on the postsynapticdopamine 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.**
- **Drug selectively affecting certain dopamine receptors may have more limited adverse effects.**

Dopamine Receptor Agonists

- **Have an important role as first-line therapy for Parkinson's disease.**
- **Have lower incidence of response fluctuations and dyskinesias.**
- **Provide less symptomatic benefit and are more likely to cause mental side effects, somnolence, and edema.**

Dopamine Receptor Agonists

- **May 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 dopamine agonists is disappointing in patients who never responded to levodopa.**

Bromocriptine

- Is a D_2 agonist.
- This drug has been widely used to treat Parkinson's disease in the past but is now rarely used fin favour of the newer dopamine agonists.

Pergolide

- It stimulates both D_1 and D_2 receptors.
- It increases “on-time” among response fluctuators.
- It permits levodopa dose to be reduced.
- Its use has been associated with clinical or subclinical valvular heart disease in one third of patients.

Pramipexole

- Is not an ergot derivative.
- It has preferential affinity for D_3 receptors.
- It is effective as monotherapy for mild parkinsonism
- It is helpful in patients with advanced disease, allowing the dose of levodopa to be reduced, and smoothing out response fluctuations.

Pramipexole

- It may ameliorate affective symptoms.
- It is able to scavenge hydrogen peroxide and enhance neurotrophic activity in mesencephalic dopaminergic cell culture and is thought to be neuroprotective.
- Rapidly absorbed after oral administration, and excreted largely unchanged in urine. Renal insufficiency require dosage adjustment.

Ropinirole

- **It is not an ergot derivative.**
- **Is relatively pure D_2 agonist.**
- **Effective in monotherapy for patients with mild disease.**
- **Is effective in smoothing the response to levodopa in patients with more advanced disease and response fluctuations.**
- **It is metabolized by CYP1A2.**

Dopamine Receptor Agonists

Adverse Effects:

A. **GIT effects:**

- **Anorexia, nausea, and vomiting (can be minimized by taking the drug with meals).**
- **Constipation.**
- **Dyspepsia, and reflux esophagitis.**
- **Bleeding from PUD.**

Dopamine Receptor Agonists

B. Cardiovascular effects:

- Postural hypotension.
- Painless digital vasospasm with long-term use of the ergot derivatives.
- Cardiac arrhythmias.
- Peripheral edema.
- Cardiac valvulopathy with pergolide.

C. Dyskinesias: like those of levodopa.

Dopamine Receptor Agonists

D. **Mental disturbances: Confusion, hallucinations, delusions and, and other psychiatric reactions which are more common and severe than with levodopa.**

- **Disorders of impulse control may occur either as an exaggeration of a previous tendency or as a new phenomenon and may lead to compulsive gambling, shopping, betting, sexual activity, and other behaviors. They relate to activation of D_2 or D_3 dopamine receptors in the mesocorticolimbic system.**

Dopamine Receptor Agonists

E. **Others:**

- **Headache, nasal congestion, increased arousal.**
- **Pulmonary infiltrates, pleural and retroperitoneal fibrosis (ergots).**
- **Erythromelalgia: consists of red, tender, painful, swollen feet, and occasionally hands, may be associated with arthralgia.**

Dopamine Receptor Agonists

- **Uncontrollable tendency to fall asleep at inappropriate times, particularly in patients receiving pramipexole or ropinirole.**
- **This requires discontinuation of the medication.**

Contraindications:

- **Psychotic illness, recent MI, PUD, and peripheral vascular disease (ergots).**

Monoamine Oxidase Inhibitors 513

- MAO-A metabolizes norepinephrine, serotonin and dopamine.
- MAO-B metabolizes dopamine selectively.
- Selegiline is a selective irreversible inhibitor of MAO-B at normal doses. At higher doses, it inhibits MAO-A as well.
- It retards breakdown of dopamine.
- Thus, it enhances and prolongs the effect of levodopa, allowing the dose of levodopa to be reduced.

Selegiline

- It may reduce mild on-off or wearing-off phenomena.
- It is used as adjunct to levodopa for patients with a fluctuating or declining response.
- Given with breakfast and lunch, and may cause insomnia if taken later during the day.
- It has a minor therapeutic effect on parkinsonism when given alone.

Rasagiline

- Another MAO-B inhibitor.
- More potent than selegiline in preventing MPTP-induced parkinsonism.
- Used for early symptomatic treatment.
- Nonselective inhibitors should not be used with levodopa because of hypertensive crisis due to accumulation of norepinephrine.

- Safinamide is a third such drug.

Monoamine oxidase B inhibitors

- **They should not be taken by patients receiving meperidine, tramadol, methadone, propoxyphene, cyclobenzaprine, and the antitussive dextromethorphan.**
- **Should not be taken with other monoamine oxidase inhibitors, tricyclic antidepressants or serotonin reuptake inhibitors because of the risk of acute toxic interactions of the serotonin syndrome.**
- **May increase adverse effects of levodopa.**

Catechol-O-Methyltransferase (COMT) Inhibitors

- **Inhibition of dopa decarboxylase has been associated with compensatory activation of other pathways of levodopa metabolism, especially COMT.**
- **COMT leads to formation of 3-O-methyldopa which competes with levodopa for active transport mechanisms responsible for transport across the intestinal mucosa and blood-brain barrier → poor therapeutic response to levodopa.**

COMT Inhibitors

- **Selective COMT inhibitors, tolcapone and entacapone, prolong the action of levodopa by reducing its peripheral metabolism → increase in levodopa bioavailability and reduction in its clearance.**
- **May be helpful in patients receiving levodopa and has response fluctuation. They lead to a smoother response, more prolonged "on-time", and reduction of levodopa total daily dose.**

Tolcapone and Entacapone

- **Entacapone is preferred because it has not been associated with hepatic toxicity.**
- **Actions are similar, both are rapidly absorbed, bound to plasma proteins and metabolized.**
- **Tolcapone has both central and peripheral effects, whereas the effect of entacapone is peripheral.**
- **t½ of both agents is ~ 2 hours.**

Tolcapone and Entacapone

- Tolcapone is more potent and has a longer duration of action.
- Stalevo = levodopa +carbidopa + entacapone. It has been associated with earlier occurrence and increased frequency of dyskinesia.
- Increased risk for cardiovascular events (myocardial infarction, stroke, cardiovascular death) is under evaluation.

Tolcapone and Entacapone

Adverse effects:

1. **Those related to levodopa.**
2. **Diarrhea and abdominal pain.**
3. **Orthostatic hypotension.**
4. **Sleep disturbances.**
5. **Orange discoloration of urine.**
6. **Tolcapone has been associated rarely with death from acute hepatic failure.**

Apomorphine

- **Is a potent dopamine agonist at postsynaptic D2 receptors in the caudate nucleus and putamen.**
- **Subcutaneous injection is effective for the temporary relief of off-periods of akinesia.**
- **Acts within 10 min of injection and action lasts up to 2 hours.**

Apomorphine

- Nausea is often troublesome and requires pretreatment with the antiemetic trimethobenzamide (maintained during therapy).
- 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.
- It should not be used in patients taking serotonin 5-HT3 antagonists because severe hypotension may result.

Amantadine

- An antiviral agent found by chance to have antiparkinsonism effects.
- It may potentiate dopaminergic function by influencing the synthesis, release, or reuptake of dopamine.
- It may antagonize the effects of adenosine at adenosine A_{2A} receptors, which may inhibit D_2 receptor function.

Amantadine

- It releases catecholamines from peripheral stores.
- It is an antagonist of the NMDA-type glutamate receptor, suggesting an antidyskinetic effect.
- Excreted unchanged in urine.
- Benefits may be short-lived, effect disappear in few weeks.

Amantadine

- Improves bradykinesia, rigidity and tremors.
- May help reduce iatrogenic dyskinesis.

Adverse effects:

1. CNS adverse reactions: restlessness, depression, irritability, insomnia, agitation, excitement, hallucinations, and confusion.
- Overdose → acute toxic psychosis, and convulsions.

Amantadine

2. Livedo reticularis (A purplish network-patterned discoloration of the skin caused by dilation of capillaries and venules).
3. Peripheral edema (not due to cardiac, hepatic, or renal disease), and responds to diuretics.
4. Headache, heart failure, postural hypotension, urinary retention, anorexia, nausea, vomiting, constipation and dry mouth.

Antimuscarinic Drugs

- Centrally-acting agents may improve tremor and rigidity of parkinsonism, with little effect on bradykinesia.
- Benztropine, orphenadrine, trihexyphenidyl.
- Adverse effects include:

1. Those due to block of acetylcholine receptor.
2. Dyskinesia.
3. Acute suppurative parotitis some times occurs secondary to dryness of the mouth.

- Withdrawal of the drug should be gradual.