

**PDA OVERVIEW:
PHARMACOLOGY OF ANTIPARKINSONIAN AGENTS**

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Reference: Chapter 20, Treatment of Central Nervous System Degenerative Disorders, pages 529-538 in Goodman and Gilman's The Pharmacological Basis of Therapeutics

I. Parkinson's Disease

A. Description

CNS disease characterized by three cardinal features.

1. Bradykinesia - slowness or lack of movement
2. Muscular rigidity - difficult for someone else to move a limb
3. Resting tremor - stops upon voluntary movement
4. Postural instability – may lead to falling accidents

B. Pathophysiology

PD is a progressive neurodegenerative disease characterized by a selective loss or degeneration of the nigrostriatal pathway – a pathway that controls motor movement and uses dopamine (DA) as the neurotransmitter.

II. Pharmacotherapy

- In theory any drug that can penetrate the blood brain barrier and cause activation of DA receptors or blockade of acetylcholine or glutamate receptors should be of value in treating Parkinson's disease.
- Current drug therapies treat only the symptoms of the disease. They do not cure or alter the course of the underlying disease.

A. L-DOPA

1. Mechanism of action

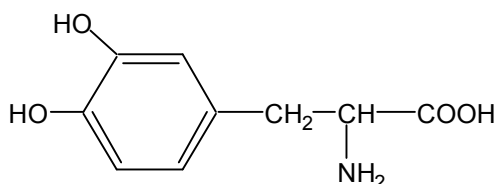
L-DOPA is the amino acid precursor to dopamine.

L-DOPA is actively absorbed

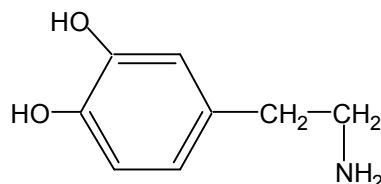
- From the GI tract (food-drug interaction possible)
- Through the blood brain barrier (BBB)
- Into the dopamine nerve terminal (loss of effect as disease progresses)

Once L-DOPA is transported into the nerve terminal, it is decarboxylated by AAADC to form dopamine. Dopamine is stored in vesicles and later released.

Apparently, there are enough surviving neurons for the synthesis and release of dopamine to occur and have a therapeutic effect.



L-DOPA



Dopamine

2. Side Effects

Side effects that occur later in therapy (2 - 4 months) include abnormal involuntary movements, nightmares, and hallucinations. These side effects result from high levels of dopamine in the CNS.

3. On-Off phenomenon

Occurs with L-DOPA in later stages of the disease.

The on portion or peak-dose dyskinesia - involuntary movements occurring at the time of peak plasma levels - too much dopamine.

The off portion or symptoms of PD – lack of dopamine.

Reason - As the disease progresses, more neurons die and receptors become supersensitive to compensate for the lack of dopamine. With fewer neurons, the synthetic and storage capabilities of dopamine are lessened. Now, the range of therapeutic plasma conc of L-DOPA becomes much more narrow. High levels of DA produce dyskinesias because of supersensitive receptors. Low levels result in PD sxs .

4. Concern

The metabolism of L-DOPA to DA generates free radicals. The production of free radicals is a form of oxidative stress that can lead to neuronal death. It's possible that L-DOPA accelerates the progression of the disease by providing a substrate for free radical formation.

5. Carbidopa

Carbidopa is a peripheral inhibitor of AAADC. When given with L-DOPA, it prevents the conversion of L-DOPA to DA in the periphery so more can get into the CNS. There is no need to form DA in the periphery – it only leads to side effects.

B. Direct Dopamine Agonists

These agents do not require bioactivation as needed with L-DOPA. Advantageous given that the site of bioactivation of L-DOPA becomes deficient in patients with PD.

Pramipexole (Mirapex®) and Ropinirole (Requip®)

Selective agonist for the D2/D3 receptors.

Gaining favor because well tolerated and may offer some advantages over L-DOPA

- longer DOA allows for less on/off and dyskinesias
- concern that L-DOPA contributes to oxidative stress leading to increased loss of DA neurons

May be used initially in mild cases to delay use of L-DOPA.

Classic DA agonist side effects: N/V, hallucinations and orthostatic hypotension

C. Anticholinergics

Anticholinergics are used as supportive or adjuncts to L-DOPA therapy. They are used in patients with mild forms of PD, or in patients who cannot tolerate or who do not respond to L-DOPA therapy. These drugs are helpful in reducing tremor but not rigidity or slowness of movement.

All anticholinergics used in the treatment of PD are equally effective. Be aware that some patients may tolerate one preparation better than another.

Benzotropine (Cogentin®) and trihexyphenidyl (Artane®) are examples.

D. COMT Inhibitors

Catechol-O-methyl-transferase is an enzyme found in the liver and at the synapse. COMT will methylate (and inactivate) any compound with a catechol nucleus (this includes L-DOPA and dopamine). The intent is to decrease the catabolism of L-DOPA so more is available to the CNS for conversion to DA and to block metabolism of DA so more remains in the synaptic cleft.

Tolcapone (Tasmar®)

Long DOA (given 2-3/d)

Acts in the periphery and CNS. Liver toxicity may be a problem.

Entacapone (Comtan®)

Short DOA (2 hrs) and is given with each dose of L-DOPA

Acts only in the periphery

Side effects of both appear minimal but tend to enhance those already seen with L-DOPA.

