Drug Therapy of Parkinsonism

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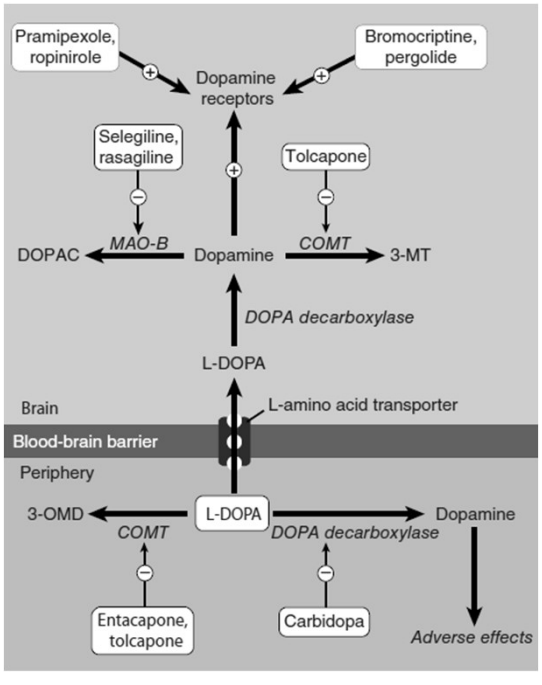
Parkinsonism is a progressive neurological disorder of muscle movement ,usually affects people over 65Y, characterized by:

- Tremors
- Muscular rigidity
- Bradykinesia

Physiology

- Normal muscle movement requires balance of dopamine (inhibitor) and ACh (stimulator)
- In the substantia nigra, enough dopamine is released to counteract the effects of Ach
- In Parkinson's disease destruction of cells in the substantia nigra results in the degeneration of the nerve terminals that secrete dopamine in the neostriatum
- This triggers a chain of abnormal signaling, resulting in loss of the control of muscle movements.



Drug used in parkinson's disease
Dopamine precursor (levodopa)

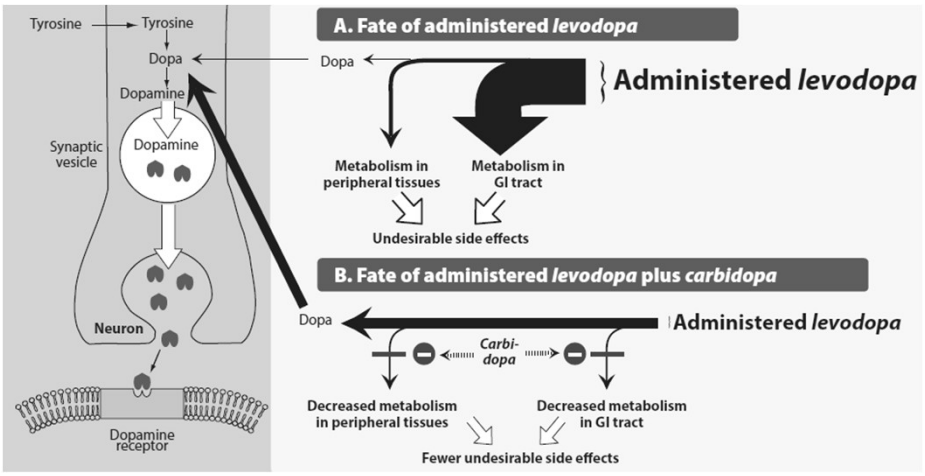
- Dopamine does not cross the blood–brain barrier, but its precursor, levodopa, is actively transported into the CNS and converted to dopamine.
- Levodopa must be administered with carbidopa. Without carbidopa, much of the drug is decarboxylated to dopamine in the periphery, resulting in nausea, vomiting, cardiac arrhythmias, and hypotension.

Carbidopa

(A dopamine decarboxylase inhibitor)

- Decrease the metabolism of levodopa in the periphery
- Increasing the availability of levodopa to the CNS.
- Lowers the dose of levodopa needed & decreases the side effects arising from peripherally formed dopamine.

Synthesis of dopamine from levodopa in the absence and presence of carbidopa



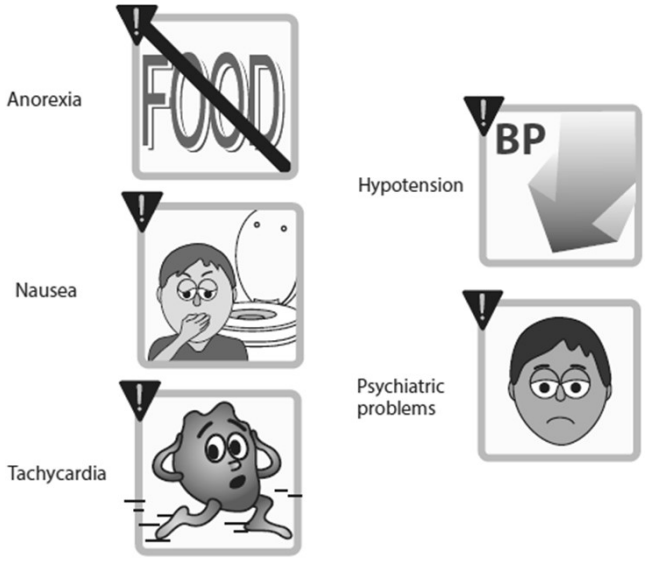
Therapeutic uses

- Levodopa used in combination with carbidopa
- Reduces the severity of symptom of parkinsonism for the first few years of treatment. but decline in response during the 3rd to 5th year of therapy occurs.
- Withdrawal from the drug must be gradual.

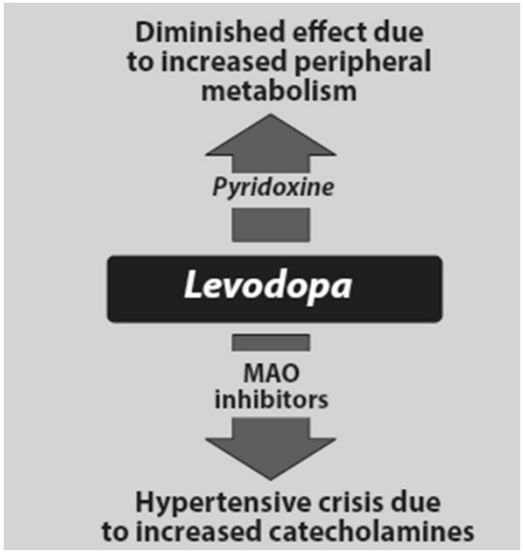
Pkarmacokinetic

- Levodopa should be taken on an empty stomach(30 minutes before a meal)
- Levodopa half-life (1 to 2 hours)

Adverse effects of levodopa



Some drug interactions observed with levodopa.
MAO = monoamine oxidase

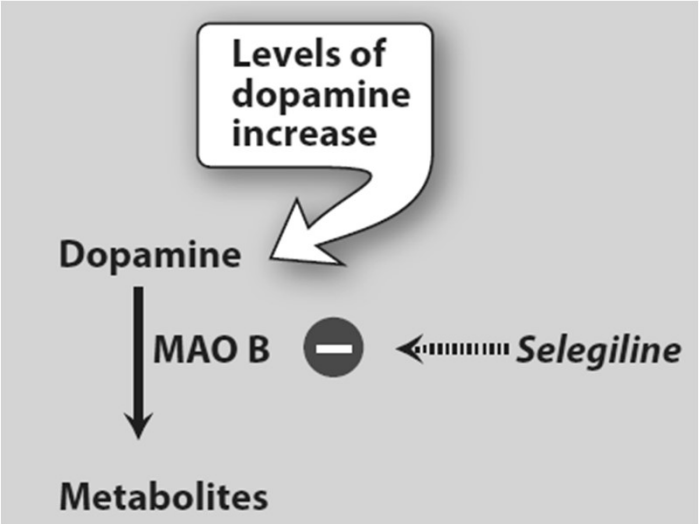


MAO inhibiters

Selegiline

- At low to moderate doses. selectively inhibits monoamine oxidase (MAO) type B (which metabolizes Dopamine) ,this lead to increases dopamine levels in the Brain
- At high doses it loses its selectivity , selegiline (inhibit MAO type A (which metabolizes norepinephrine and serotonin)
- Selegiline is metabolized to methamphetamine and amphetamine, whose stimulating properties may produce insomnia if the drug is administered later than mid-afternoon.
- It has little potential for causing hypertensive crises

Action of selegiline in dopamine metabolism.



Catechol-O-methyltransferase inhibitors
Entacapone and tolcapone

- Selectively and reversibly inhibit COMT **(**the enzyme in both the CNS and peripheral tissues , converts levodopa to 3-O-methyldopa)

- Inhibition of COMT by these agents leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of levodopa, and greater concentrations of brain dopamine
- Entacapone acts only in the periphery.
- Tolcapone is taken 3 times daily
- Entacapone 5 times daily

Adverse effects of Entacapone and tolcapone

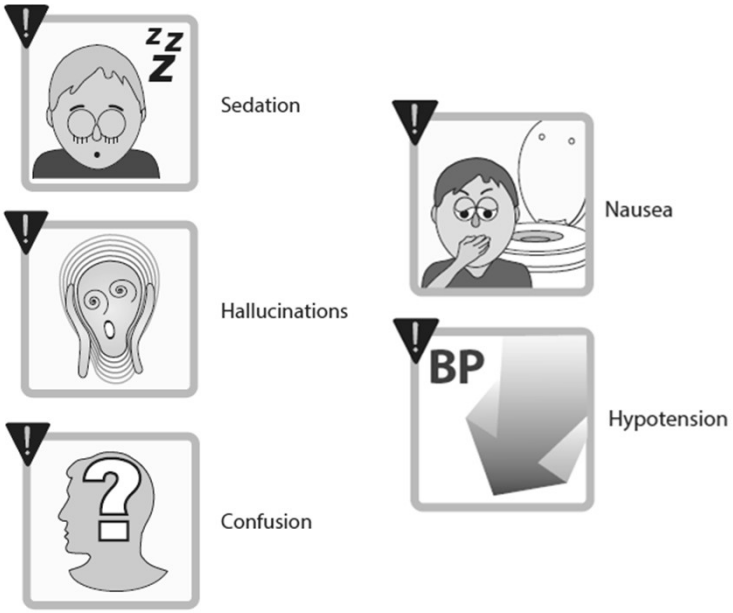
- Diarrhea, postural hypotension, nausea, anorexia, dyskinesias, hallucinations, and sleep disorders
- Hepatic necrosis (tolcapone)

Dopamine-receptor agonists

Bromocriptine

- An ergot alkaloid
- Acts as a partial agonist at dopamine D2 receptors in the brain.
- The drug increases the functional activity of dopamine neurotransmitter
- Used as individual therapy or in combinations with levodopa (and with anticholinergic drugs)

Some adverse effects of dopamine agonists



Adverse effects of Bromocriptine

- Anorexia, nausea and vomiting
- Dyskinesias, and postural hypotension
- Behavioral effects, confusion, hallucinations

NOTE: its use decrease with the introduction of non-ergot dopamine receptor agonists.

Pramipexole

- Non-ergot has high affinity for the dopamine D3 receptor.
- Used as monotherapy or with levodopa in advanced disease.
- Pramipexole is administered orally 3 times daily

Adverse effects of Pramipexole

- Anorexia, nausea and vomiting, postural hypotension, and dyskinesias.
- Mental disturbances (confusion, delusions, hallucinations,)

Note : The drug is contraindicated in patients with active peptic ulcer disease, psychotic illness, or recent myocardial infarction.

Ropinirole

- Non-ergot, this drug has high affinity for the dopamine D2 receptor.
- Monotherapy or with levodopa
- It is given 3 times daily, but a prolonged release form can be taken once daily.
- Similar adverse effects and contraindications to those of pramipexole.

Apomorphine

- A potent dopamine receptor agonist
- Injected subcutaneously may provide rapid (within 10 min) but temporary relief (1–2 h) of "off-periods" of akinesia in patients on optimized dopaminergic therapy.

Adverse effects of Apomorphine

- Severe nausea(pretreatment for 3 days with antiemetics is necessary)
- Dyskinesias, hypotension, drowsiness, and sweating

Amantadine

- Enhances dopaminergic neurotransmission by unknown mechanisms (increasing synthesis or release of dopamine or inhibition of dopamine reuptake)
- Improve bradykinesia**,** rigidity, and tremor(for only a few weeks).
- It has muscarinic blocking actions
- Amantadine also has antiviral effects.

Adverse effects of Amantadine

- Restlessness, agitation, insomnia, confusion, hallucinations, and acute toxic psychosis.
- Dermatologic reactions
- Gastrointestinal disturbances
- Urinary retention
- Postural hypotension.
- peripheral edema

Acetylcholine-Blocking (Antimuscarinic) Drugs
Benztropine

- Decrease the excitatory actions of cholinergic neurons on cells in the striatum by blocking muscarinic receptors.

Adverse effect

- Drowsiness, confusion, &hallucinations.
- Peripheral adverse effects are typical of atropine-like drugs.