Drugs Used in Parkinsonism & Other Movement Disorders

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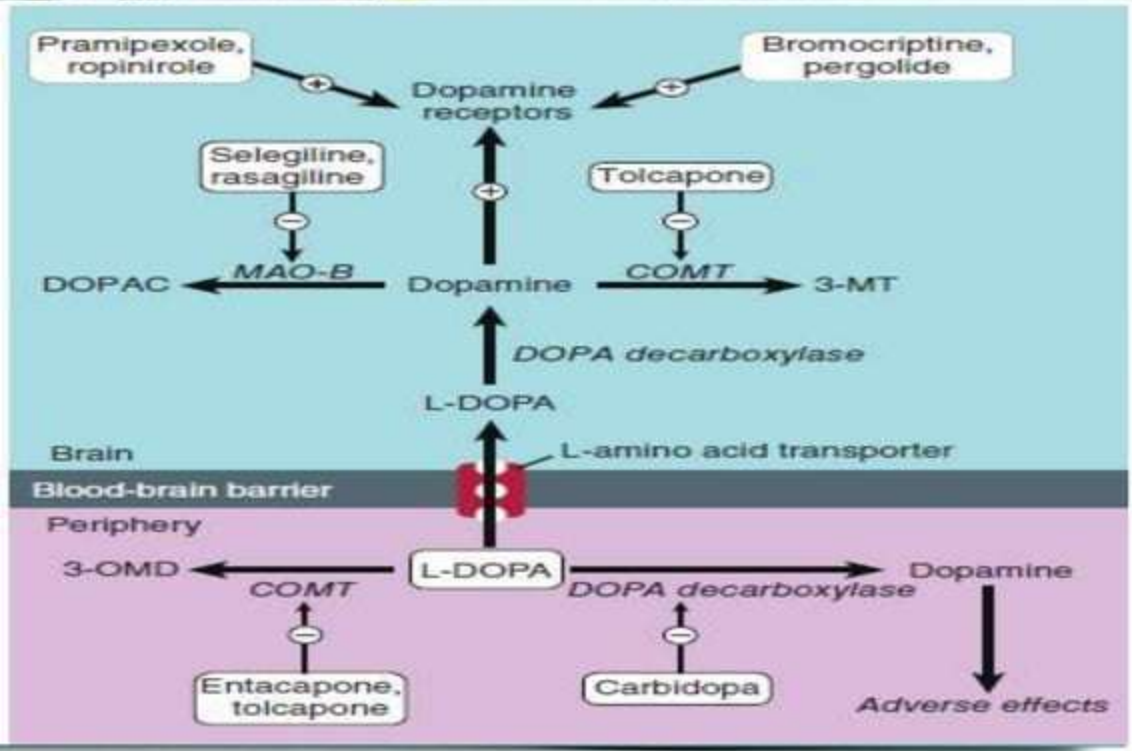
PARKINSONISM

- Parkinsonism (paralysis agitans) is a common movement disorder that involves dysfunction in the basal ganglia and associated brain structures.
- Signs include rigidity of skeletal muscles, akinesia (or bradykinesia), flat facies, and tremor at rest (mnemonic **RAFT**).
- ***1. Naturally occurring parkinsonism***
- ***2. Drug-induced parkinsonism***

DRUG THERAPY OF PARKINSONISM

- **A. Levodopa**
- ***1. Mechanisms:*** Because dopamine has low bioavailability and does not readily cross the blood-brain barrier, its precursor, l- dopa (levodopa), is used.
- This amino acid enters the brain via an l-amino acid transporter (LAT) and is converted to dopamine by the enzyme aromatic l-amino acid decarboxylase (dopa decarboxylase), which is present in many body tissues, including the brain.


Pramipexole, ropinirole
Bromocriptine, pergolide
Dopamine receptors
Selegiline, rasagiline
Tolcapone
DOPAC
MAO-B
Dopamine
COMT
3-MT
DOPA decarboxylase
L-DOPA
Brain
L-amino acid transporter
Blood-brain barrier
Periphery
3-OMD
COMT
L-DOPA
DOPA decarboxylase
Dopamine
Entacapone, tolcapone
Carbidopa
Adverse effects

Toxicity

- Most adverse effects are dose dependent.
- Gastrointestinal effects include anorexia, nausea, and emesis and can be reduced by taking the drug in divided doses.
- Tolerance to the emetic action of levodopa usually occurs after several months.
- Postural hypotension is common, especially in the early stage of treatment.
- Other cardiac effects include tachycardia, asystole, and cardiac arrhythmias (rare).
- Dyskinesias occur in up to 80% of patients.

B. Dopamine Agonists

- ***1. Bromocriptine***—An ergot alkaloid, bromocriptine acts as a partial agonist at dopamine D2 receptors in the brain.
- The drug increases the functional activity of dopamine neurotransmitter pathways, including those involved in extrapyramidal functions

- Common adverse effects include anorexia, nausea and vomiting, dyskinesias, and postural hypotension.
- Behavioral effects, which occur more commonly with bromocriptine than with newer dopamine agonists, include confusion, hallucinations, and delusions.
- Ergot-related effects include erythromelalgia and pulmonary infiltrates.

- ***2. Pramipexole:***
- This non-ergot has high affinity for the dopamine D3 receptor.
- Pramipexole is administered orally 3 times daily and is excreted largely unchanged in the urine.
- The dose of pramipexole may need to be reduced in renal dysfunction.

- Adverse effects include anorexia, nausea and vomiting, postural hypotension, and dyskinesias.
- Mental disturbances (confusion, delusions, hallucinations, impulsivity).

3. Ropinirole

- Another non-ergot, this drug has high affinity for the dopamine D2 receptor.
- The standard form is given 3 times daily, but a prolonged release form can be taken once daily.
- Ropinirole is metabolized by hepatic CYP1A2, and other drugs metabolized by this isoform (e.g, caffeine, warfarin) may reduce its clearance.

4. Apomorphine

- A potent dopamine receptor agonist, apomorphine 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.

C. Monoamine Oxidase Inhibitors

Mechanism:

- **Selegiline** and **rasagiline** are selective inhibitors of monoamine oxidase type B, the form of the enzyme that metabolizes dopamine.

Toxicity and drug interactions:

- Adverse effects and interactions of monoamine oxidase inhibitors include insomnia, mood changes, dyskinesias, gastrointestinal distress, and hypotension.
- Combinations of these drugs with meperidine have resulted in agitation, delirium, and mortality.

D. Catechol -*O*- methyltransferase (COMT) Inhibitors

Mechanism of action:

Entacapone and **tolcapone** are inhibitors of COMT, the enzyme in both the CNS and peripheral tissues that converts levodopa to 3-*O*-methyldopa (3OMD).

Clinical uses:

- The drugs are used as adjuncts to levodopacarbidopa, decreasing fluctuations, improving response, and prolonging "on-time."
- Tolcapone is taken 3 times daily, entacapone 5 times daily.

Toxicity:

- Adverse effects related partly to increased levels of levodopa include dyskinesias, gastrointestinal distress, and postural hypotension.
- Other side effects include sleep disturbances and orange discoloration of the urine.

E. Amantadine

Mechanism of action:

- Amantadine enhances dopaminergic neurotransmission by unknown mechanisms that may involve increasing synthesis or release of dopamine or inhibition of dopamine reuptake.
- The drug also has muscarinic blocking actions.

Pharmacologic effects:

- Amantadine may improve bradykinesia, rigidity, and tremor but is usually effective for only a few weeks.
- Amantadine also has antiviral effects

Toxicity:

- Behavioral effects include restlessness, agitation, insomnia, confusion, hallucinations, and acute toxic psychosis.
- Dermatologic reactions include livedo reticularis.
- Miscellaneous effects may include gastrointestinal disturbances, urinary retention, and postural hypotension.
- Amantadine also causes peripheral edema, which responds to diuretics.

F. Acetylcholine-Blocking (Antimuscarinic) Drugs

Mechanism of action:

The drugs (e.g, benztropine, biperiden, orphenadrine) decrease the excitatory actions of cholinergic neurons on cells in the striatum by blocking muscarinic receptors.

- ***Pharmacologic effects***—These drugs may improve the tremor and rigidity of parkinsonism but have little effect on bradykinesia.
- ***Toxicity***—CNS toxicity includes drowsiness, inattention, confusion, delusions, and hallucinations.

DRUG THERAPY OF OTHER MOVEMENT DISORDERS

Huntington's Disease:

- An inherited adult-onset neurologic disease characterized by dementia and bizarre involuntary movements.

- Drug therapy usually involves the use of amine-depleting drugs (e.g, **reserpine**, **tetrabenazine**), the latter having less troublesome adverse effects.
- Dopamine receptor antagonists (e.g, **haloperidol, perphenazine**) are also sometimes effective and olanzapine is also used.

Tourette's syndrome

- Tourette's syndrome is a disorder of unknown cause that frequently responds to haloperidol and other dopamine D2 receptor blockers, including pimozide.
- Though less effective overall, carbamazepine, clonazepam, and clonidine have also been used.

Drug-Induced Dyskinesias

- In acute dystonias, parenteral administration of benztropine or diphenhydramine is helpful.
- **Tardive dyskinesias** that develop from therapy with older antipsychotic drugs are possibly a form of denervation supersensitivity.

Wilson's Disease

- This recessively inherited disorder of copper metabolism results in deposition of copper salts in the liver and other tissues.
- Hepatic and neurologic damage may be severe or fatal.
- Treatment involves use of the chelating agent **penicillamine** (dimethylcysteine), which removes excess copper.
- Toxic effects of penicillamine include gastrointestinal distress, myasthenia, optic neuropathy, and blood dyscrasias.
- **Trientine** and **tetrathiomolybdate** have also been used.

Restless Legs Syndrome

- This syndrome, of unknown cause, is characterized by an unpleasant creeping discomfort in the limbs that occurs particularly when the patient is at rest.
- The disorder is more common in pregnant women and in uremic and diabetic patients.
- Dopaminergic therapy is the preferred treatment, and both **pramipexole** and **ropinirole** are approved for this condition.

Thank You