Anti-Parkinson Drugs

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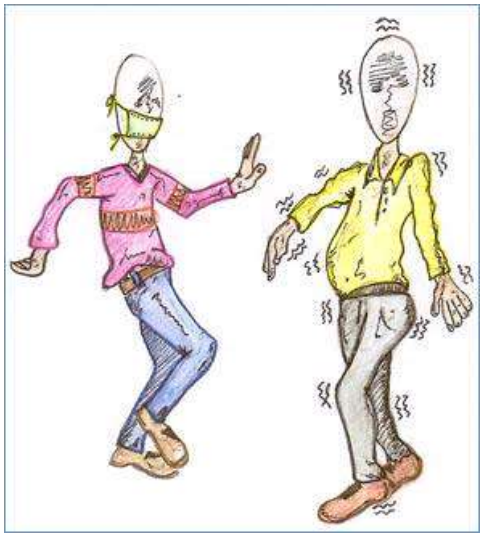


Anti-Parkinson Drugs

Pathogenesis:

- Imbalance between cholinergic & dopaminergic neurotransmission
- Degeneration of nigrostriated dopaminergic neurons, substantia nigra & corpus pallidum that control & coordinate motor activity

L-dopa

crosses brain barrier and converts to

dopamine

stimulates

D2 receptors

inhibits

adenylyl cyclase

reduces

reduces

Ca2+ channel

closes

IP3

cyclic AMP

decreases

intracellular Ca2+

inhibits

firing of striatal cholinergic nerves

restores balance

treats

Parkinson's Disease

reduced dopamine in Parkinson's

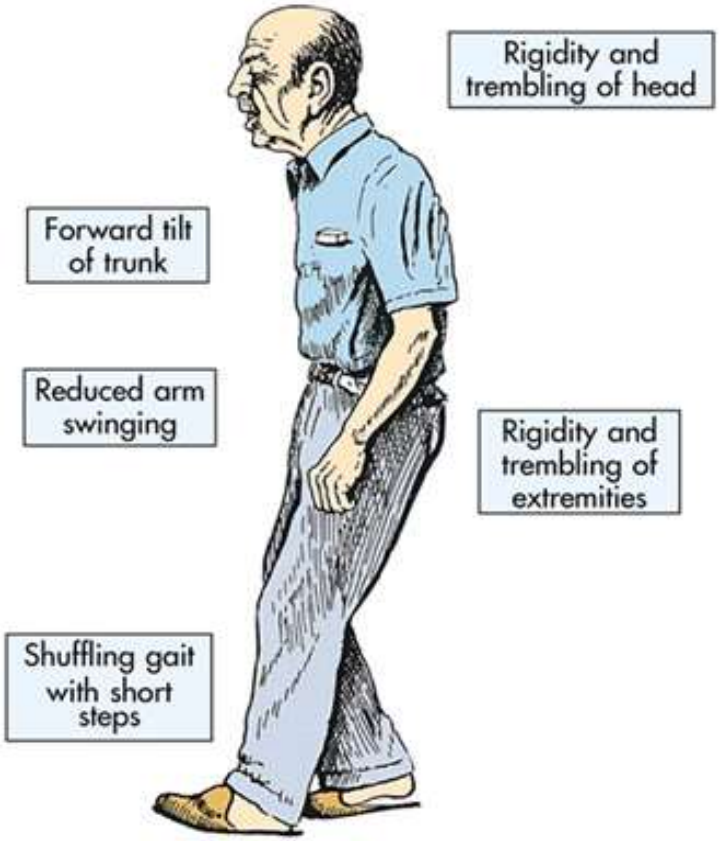
cholinergic overactivity

susbtantia nigra dopamine

corpus striatum cholinergic

Manifestations

- Involuntary movements
- Rigidity
- Tremor
- Bradykinesia
- Postural instability
- Dementia



Causes

- Unclear
- A number of factors may have a role:
  - Environmental – toxins
  - Free Radicals – there is a increase in post-mortem brain sections
  - Aging – age related decline in dopamine production
  - Genetic – possible, no single gene identified
  - Traumatic (e.g. in boxers).

The Drugs

It is palliative not curative & includes:

- **Dopaminergic drugs (improving dopamine functioning):**
  - Levodopa (Dopamine precursor)
  - Bromocriptine (Dopamine receptor agonists)
  - Amantadine (Increase synthesis & release)
  - Selective monoamine oxidase B inhibitors
  - Catechol-O-methyltransferase inhibitors
- **Antimuscarinic drugs**
  - useful in mild cases & in drug-induced parkinsonism (by phenothiazines)
- **Drug combination**

Drug therapy…..cont

- Dopaminergic drugs improve bradykinesia & rigidity
- Anti-cholinergic agents improves rigidity & tremor

Levodopa

- Dopamine is ineffective because it is metabolized enzymatically in GIT & liver & does not cross BBB
- L-dopa is a natural AA precursor of dopamine & crosses actively BBB
- Converted by remaining neuron (20%) into dopamine

Levodopa

- Peripheral decarboxylation of L-dopa occurs and produces peripheral adverse effects as nausea, vomiting & hypotension
- So, peripheral decarboxylation of L-dopa should be prevented to reduce these peripheral adverse effects

- Carbidopa and benserazide are examples

Preparations

- Levodopa + carbidopa → Sinemet
- Levodopa + benserazide → Co-beneldopa
- Decarboxylase inhibitors do not cross BBB so decreases levodopa dose

Pharmacokinetics

- Absorbed by the small intestine by an active transport system
- Good GI absorption on empty stomach
- High protein diet impairs absorption
- t ½ 1-2 hours

Adverse effects

- Peripheral
- N, V (prevented by cyclizine)
- Postural hypotension
- Arrhythmias

Adverse effects

- **Central:**
- Involuntary movements
  - dyskinesia, restlessness, choreo-athetosis
- Mental changes:
  - Hallucination, confusion & agitation like psychosis (due to increased dopamine levels in the cortex and limbic system).

Adverse effects

- End-of dose deterioration
  - Due to rapid disappearance of dose effects.
  - corrected by small frequent doses
- On-off phenomenon:
  - ON phase at the start of treatment (good control of Parkinson symptoms but dyskinesia & agitation are obvious)
  - OFF phase: severe Parkinson features due to sudden disappearance of dose effect
  - corrected by apomorphine.

Drug interactions with L-dopa

- Nonselective MAOI+ levodopa …….
  Hypertensive crisis (↑ NE)
- Pyridoxine (B6) + levodopa …….
  Attenuation of effects due to increased peripheral metabolism (not in the presence of decarbo inhibitors)
- Levodopa is used cautiously in; glaucoma, heart disease (arrhythmias) & psychosis

Amantadine (dopamine release)

- is an anti-virus agent against influenza, used as adjuvant therapy for dyskinesis effects
- Increases synthesis and release of dopamine & decreases reuptake
- it also has slight antimuscrinic effects

Amantadine (dopamine release)

- improves bradykinesia & rigidity
- effects are < Levodopa > anti-muscarinics effects

Pharmacokinetics

- Well absorbed
- It has long ½ life
- Execrated unchanged by the kidney

Bromocriptine (parlodel)

- is an ergot alkaloid
- acts as a dopamine agonist on D2 receptors also a weak α-adrenoreceptor antagonist
- used mainly with levodopa
- start at low dose then increased gradually weekly (2-3 months)

Bromocriptine (parlodel)

- oral, rapid absorption
- t ½ 5 hours
- useful in patients with End-of dose deterioration with levodopa (to overcome the rapid disappearance of L-Dopa effects)

Adverse effects

- N, V,
- Postural hypotension (alpha blocking)
- Confusion
- Hallucination
- Insomnia

Selegiline (Deprenyl)

- is a selective, irreversible MAO B inhibitor; increase dopamine in brain tissues
- increases effects of levodopa & decreases its dose
- useful in End-of dose deterioration with levodopa

Selegiline (Deprenyl)

- Early stage-prescribed on its own to delay need for Levodopa and there is good evidence for its slowing down of PD progression (protect neurons)

Adverse effects

- Nausea, vomiting constipation, dry mouth
- insomnia & increases ABP with high doses
- does not produce cheese-drug interaction (tyramine is metabolized by MAO A)

Apomorphine

- is a derivative of morphine
- acts as an agonist at D1 & D2 receptors
- useful in Parkinson's disease with On-OFF phenomenon
- given sc or IV infusion
- may cause N, V & respiratory depression
- rapid onset with a short duration of action

Adverse effects

- N and V
- Dyskinesia (D1 effect)
- Hallucinations
- Respiratory depression
- Peripheral vasospasm (Raynaunds)

Central Anti-muscarinics

- **Benzhexol, Orphenadrine, Benztropine, Procyclidine**
- Cross well BBB
- They improve tremor, rigidity & sialorrhoea (not bradykinesia)
- Useful in mild case
- Oral and IM or IV in acute drug-induced dystonia reactions or parkinsonism.

Drugs to avoid

Generic Name	Prescribed for
Prochlorperazine	N +V, Dizziness
Prephenazine	Depression
Flupentixol	Confusion, Hallucinations
Chlorpromazine	“
Pimozide	“
Sulpiride	“