

ANTI-PARKINSONIAN DRUG.

- tremor, Rigidity, bradykinesia, loss of postural Reflexes.
 - due to dopamine containing neurons in substantia nigra, → Result is dopamine def.

CLASSIFICATION - Refer Kd t

Dopamine precursors → Levodopa

- L-dopa main drug for Parkinsonism.
- converted to dopamine by decarboxylase enzyme in the dopaminergic neurons of striatum

↓
bind with D₂ Receptor in the basal ganglia to produce Antiparkinson effect.

Metabolic Pathway

In Periphery

① Levodopa is metabolized by: → Dopa decarboxylase

L-Dopa $\xrightarrow{DDC}$ DA

$\xrightarrow{COMT}$ 3OMD. (3, O-Methyldopa)

Inhibitors used

Entacapone / Tolcapone inhibit COMT → ↓ 3OMD
→ ↑ Levodopa BA

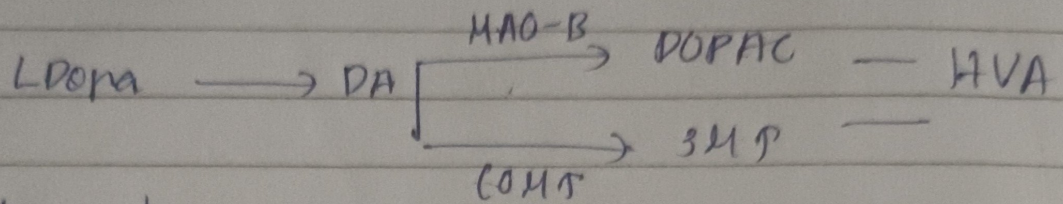
D₁D₅ → ~~Levodopa~~

MAO-B - Monoamine Oxidase B

HVA - Homovanillic Acid

Brain Metabolism

→



Inhibits used

- Selegiline Inhibits MAO-B
- Tolcapone Inhibits COMT

PK:

orally → Absorbed from ST

give 30-60 min before meal

metabolic product → HVA & DOPAC

↳ excrete in urine

About 1% of Administered L-Dopa enter brain

$t_{1/2} = 1-2h$

ACTIONS:

- 1) **CNS:** improve parkinsonism.
Resolves - Hypokinesia, posture, gait, speech, facial expression, mood,
- good Allergic Response.
- Action D₂ And D₁ Result in smoothing movements.
- 2) **CNS:** cause tachycardia, Arrhythmias.
postural hypotension.
- 3) **GTZ** → Nausea And vomiting

4) Endocrine: Inhibit prolactin release
↑ GH levels

ADRs:

* At the initiation of therapy: - NV
- Postural hypotension

- Cardiac Arrhythmias
- Exacerbation of Angina
- Alteration in taste sensation

* After prolonged therapy:

→ Abnormal movements (Dyskinesia)

→ Behavioural effects - Anxiety, nightmarish
severe depression, hallucinations

→ Fluctuation in motor performance.

After 3-5 years of therapy with prolonged disease
control become difficult and fluctuation in symptom
occurs.

→ Wearing off is due to ↓ in Plasma C₀ of L-Dopa
towards end of a dose.

→ Partial On/Off Response - being off and
being on (Relief of most of the symptoms but
with disabling dyskinesia).

→ called on/off phenomenon

End of dose deterioration can be improved by
Administering L-dopa in smaller doses

INTERACTION:

- Pyridoxine Abolish the therapeutic effect of levodopa
- ⇒ Antihypertensive cause severe postural hypotension

CARBIDOPA AND BENZERAZIDE

They are peripheral decarboxylase inhibitors

- They do not penetrate BBB and do not inhibit conversion of levodopa to DA in the brain.
- Administered along with levodopa, they ↑ the $t_{1/2}$ is phosphoryl make a large fraction of it available to cross BBB.

The combination is given as "Co-Carbidopa"

Benefits of the combination

- 1) The plasma $t_{1/2}$ of levodopa is prolonged
- 2) systemic conc of DA is reduced nausea and vomiting are minimized permitting faster dose escalation
- 3) Cardiac complications ↓
- 4) Pyridoxine Reversal of levodopa effect down to zero
- 5) On-off effect is minimized

Problems not Resolved

- | | |
|------------------------------|-----------------------------|
| 1) Involuntary movements | 3) Excess sleep in day time |
| 2) Behavioural Abnormalities | 4) Postural Hypotension |