Anti-parkinsons drugs

Classification → 1. Drug affecting dopaminergic syst. (↑ activity)

(a) precursor of dopamine → L-dopamine (L-dopa)

(b) peripheral de carboxylase inh → carbidopa, Benserzide

(c) Dopamin Agonist → Bromocryptine, Pergolyte
Pirib edil, Lisuride
Ropinirole, Pramiperole

(d) MAO_B inhi → Selegiline, Rasigiline

(e) COMT - inhi → Tolcapone, Entecapone

(f) Dopamine facilitators → Amantadine

(2.) Drug affecting cholinergic brain system →

(a) C.N.S anticholine → Tri-hexiphenydile
(Benz-hexole)
procyclidine, Biperiden

(b) Anti-Histaminics → orphinedrin, promethazine

Levo-dopa → Pro-drug of dopamine.

MOA levo-dopa → it is metabolic precursor of dopamine it crosses the B.B.B by an active process mediate by a carrier of aromatic amino acid.

This process may be inhibited by protein rich diet.

⇒ dopamine itself does not cross B.B.B and hence is ineffective. Brains of parkinsonism patient treated with l-dopa till death had dopamine level higher than those not so treated. further those patient who has responded well had higher dopamine level.

Pharmacokinetics → it is well absorbed from the small intestine by active transport but much of it inactivated by MAO in the wall of intestine, about 90% of absorbed drug is converted to dopamine in peripheral tissue where dopa decarboxylase are in abundant. less than 1% of administered dose enters the brain where it is converted to dopamine.

Anti parkinsonism effect of l-dopa depends on dopamine formation in the brain and hence its ability to enter brain.

∴ peripheral dopamine is not effective

carbidopa → it is peripheral dopa decarboxylase inhibitor. it can not enter brain thus carbidopa minimizes peripheral conversion of levo-dopa to dopamine and maximize the availability of l-dopa for transport to the brain.

Adverse effect -> the two main unwanted effect of L-dopa

a. involuntary choriaform movement (occurs in most patient within 2 years)

b. unpredictable on off effect (worshiny of parkin. syn. as hypokinesia, Rigidity some other unwanted effect are nausea & Anorexia and hypotension.

psychological effect such as schizophrenia with delution, Hallucination. (due to ↑ in dopamine activity, occurence of confusion dyskinesia, insomnia, nightmares) this L-dopa causes hypotension (not hypertension).

excitotoxicity of park. is cause of parkinso →

1. Dimentia is one the result of excitotoxicity is Result in neurodegeneration and condition like dementia (Alzemers dis.), ischamic brain dammage (stroke) and parkinson dis.
the excito. due to →

(a) Activation of NMDA rec. and other types of excitatory amino acid rece.

(b) Sustain rise in intra. cellular Ca^{++} concentration Ca-overload.

(c) Pathological condition (cerebral Ischemia) in which excesive Glutamate release occurs.

(d) Chemical such as Kanic acid invironmental chemical. all these region causes cell death. by various mechanism is activation of proteases formation of free

radical.

- lipid peroxidation, formation of NO and arachidonic acid

Metabolism of levo-dopa → A high protein content of a meal interfare the absorbtion of l-dopa. the drug is best taken half an hour befor or 1 hr after meal.
it is metabolites by both MAO and COMT.
its principle metabolite Homovelinic acid.
Some of the drug is converted (HVA) to nor-adrenile since the urinary excretion of vanilil mendalic acid (VMA). and 3, Methoxy 4-hydroxy-phenyl glycol (MHPG).

Drug interaction → MAO inh, may precipitate severe hypertension.

- pyridoxin accelerate the peripheral de-carboxylating of l-dopa.
- Reserpine and Phenothiazine block the effect of dopamine.
- Methyl-dopa intensified the adverse effect of l-dova.
- Sympathomimetic and Isoprenaline should be avoided in patient on l-dopa.
- because l-dopa ↑ the C.V.S toxicity of halothane
- Anticholinergic ↑ the stay of l-dopa in the stomach and ↑ its degradation. they should be taken if needed 2 hrs befor l-dopa.

COMT inh → Talcapone :- MOA :- inhibit COMT, this drug ↓ the central and peripheral metabolic degradation of l-dopa and prolongs $t_{1/2}$.

Adverse eff → orthostatic hypotension, Dyskinesia Diarrhoea, induction of hallucination due to ↑ in the serum level of l-dopa produces serious hepato-toxicity

Entakapone → less hepatotoxic than talcapone.

Dopamine Agonist →

Bromocryptin → It is an ergot alkaloid dopamine receptor agonist partial antagonist for α-receptor.

Action of bromocryptin is similar to L-dopa, but it have more side effects.

Bromocryptin also activate, dopamine receptor in the Tubero infundibular dopaminergic system in pituitary gland resulting in the secretion of prolactin inhibitory factor from hypothalamus. Secretion of PIF supresis the release of prolactin from anterior pituitary.

=> other dopaminergic receptor are Lisuride Pergolyte, pitibedile.

(Dopamine Releasing agent)

Amantadin → Amantadin is a antiviral agent, used for the treatment of influenza. it also possess antipark. agent.

=> The mechanism of action of amantadin is not clear but it has been suggested that it might alter dopamine release.

=> Amantadin is less potent that L-dopa.

adverse effect of amantadin are depression, insomnia, agitation, confusion.

=> overdoses may produce an acute cycosis.

MAO inhibitor →

Selegiline → Two types of MAO enz have been distinguish. $MAO_{(a)}$ is responcible for metabolism of Epinephrin and norepinephrin whereas $MAO_{(b)}$ is responcible for metabolism of Dopamine.

Selgine is the selective $MAO_{(b)}$ inhibitor.

Rasagiline (b) by inhibiting MAO enz, Selegiline enhancing and prolong the antiparkinsonism effect of Dopamine and l-dopa. Therefor it is used as adjunctive therapy means should be (सहयोगी) given with l-dopa.

⇒ it should not be given to those patient who are taking TCA (Tri cyclic Antidepressant) or Serotonin reuptake inhibitor because of the risk of toxic interaction.

⇒ Selegeline has only minor therapeutic effect on parkinson when given alone.

(E) Antichalinergic drug (Antimuscarinic drug) → Anti. drug were widely used for the treatment of Par. di. befor the discovery of l-dopa.

several antimuscarinic agent which are used for parkinson dise have been identified such as, Biperiden, procyclidin Benzatropin.

Anticholiner. drug should be avoided in patient with, Glaucoma, (close angle) GIT disease.

Adverse effect of Anti drug are Tachicardia Midriasis, dryness of mouth, drowsiness constipation, urinary retention,