Anti Parkinson's drugs

- Learning objectives

- **Definition of Parkinson disease and pathophysiology**

- **cholinergic and dopaminergic mechanism in Parkinson disease**

- **drugs useful in disease ;L-dopa, decarboxylase inhibitors ,dopamine agonists as Bromocriptine .**

Anti Parkinson's drugs

- Parkinson's disease
  is a progressive neurological disorder of motor movement characterized by
  tremor,
  rigidity ,
  and bradykinesia .
- it is caused by degeneration of the substantia nigra in the mid brain , and consequent loss of dopamine-containing neurons .

- In Parkinson's disease there is degenerative loss of dopaminergic neurons , and the symptoms and signs of the disease are due to dopamine depletion .

Anti Parkinson's drugs

- Certain drugs also produced the features of Parkinson's disease , most common , Fluphenazine ,Trifuoperazine and Haloperidol (Anti psychotic drugs)
- the general term Parkinsonism is used to cover both the disease and the drug –induced state .
- In Extapyramidal system ,there are two balance systems are important , on depend on Acetylcholine and the other depend on dopamine

Treatment of Parkinson's disease

- The treatment is restore dopaminergic/cholinergic balance either by
- **1:-** Reduce the cholinergic activity

  by central anti muscarinic drugs ,this is most effective in treatment of tremor and rigidity ,and less effective in treatment of bradykinesia .
- **2:-** Enhancement of dopaminergic activity either by :-
- **A:-** Replenish neuronal dopamine by supplying Levo- dopa (natural precursor of dopamine),administration of dopamine itself is ineffective as it does not cross the BBB, and because it is rapidly metabolized in the gut, blood and liver by MAO & COMT .

Treatment of Parkinson's disease

- **B:-** Inhibition metabolism of dopamine by Selegiline and prolong its action
- **C:-** Giving dopamine agonist e.g. Bromocriptine .
- **D:-** Release dopamine from nerve endings and inhibit its re-uptake by Amantadine .
- **E:-** Inhibition the catechol amin-O- methyl transferase (COMT) ,by Tolcapone .

Treatment of Parkinson's disease

- Both approaches are effective in therapy and may usefully be combined
- Dopamine doesn’t cross BBB, but its precursor L-dopa is rapidly transported into CNS and convert to dopamine by dopa decarboxylase in the brain .
- Large doses of L-dopa are needed ,because much of the drug is decarboxylated in the peripheral tissues to dopamine ,result peripheral side effects ,and only 1-5% of an oral dose of L-dopa reaches the brain
- These side effects include nausea , vomiting , postural hypotension , and even cardiac arrhythmias .

Treatment of Parkinson's disease

- Can overcome on this problem by using decarboxylase inhibitors which don’t enter the CNS ,so that they prevent only the extra cerebral metabolism of L-dopa including
- Carbidopa and Benserazide ; these two drugs are given in combination with L-dopa .
- This combination produce the same brain concentration as with Levo-dopa alone ,but only 25% of the dose is required , which is smoothest the action of L-dopa and reduce the incidence of adverse effects

- L-dopa is absorbed rapidly from small intestine especially when it is empty ; it has short half life (1-2 hours.) ,it causes fluctuation in plasma level , this is called (on-off phenomena) .
- **Adverse effects :-**
- **Peripheral side effects include :**
- **A)** Nausea ,anorexia , vomiting .
- B) Tachycardia , cardiac arrhythmias and hypotension .
- C) Mydriasis ,due to adrenergic action on irris .
- D)Blood dyscrasia ,with +ve coombs test .
- E) Brown discoloration of saliva and urine ,because dopamine stimulates secretion of melanin pigment.
- **Central side effects include :-**
- A)Visual and auditory hallucination .
- B) Abnormal involuntary movement with depression and anxiety .

Drug interactions and contraindications

- **1)** With vitamin B6 (pyridoxine),lead to increase the peripheral breakdown of L-dopa .
- 2)With MAOIs → might cause hypertensive crisis .
- **Contraindications :-**
- 1:- Psychotic patients or those taking anti psychotic drugs .
- 2:- Glaucoma ,because it increase I.O.P. .
- 3:- Contraindication in patients with cardiac diseases .

Bromocriptine

- It is a D2 receptors agonist ,also has a weak α-adrenoceptor antagonist ,commonly used in combination with L-dopa ,rapidly absorbed from gut ,has more half life than L- dopa ,so it has a smoother action than L –dopa .

- **Side effects :-** nausea ,vomiting ,hypotension ,dizziness and syncope ; with prolong use lead to pleural effusion and retroperitoneal fibrosis .

Treatment of Parkinson's disease

Amantadine :-

Is an anti viral drug used for treatment of flu. It acts to enhance synthesis , release & prevent re-uptake of dopamine ,it has little effect on tremor ,but more effective against rigidity and bradykinesia ; in toxic dose causes psychosis ,urine retention, and dry mouth .

Selegiline :-

It is MAO inhibitor, increase dopamine level in the brain and increase the action of L-dopa when administrated together with decrease the required dose .

Treatment of Parkinson's disease

Tolcapone :-

Inhibitor for COMT ,lead to increase the central up-take of L-dopa and greater concentration is in the brain .

Antimuscarinic drugs :-

They act by block Ach. receptors in the CNS, e.g. Benzhexol, Benztropine ,Orphenadrine ,& Procyclidine ; they are produce improvement in tremor ,rigidity ,sialorrhoea, muscular stiffness and leg cramps ,but little in hypokinesia .

Side effects :- blurred vision ,dry mouth ,increase I.O.P., tachycardia , urine retention ,& constipation .