Antipsychotic drugs

Also called Neuroleptics and major tranquilizers

They are effective in the treatment of schizophrenia. They are also useful in psychosis associated with depression and mania and the treatment of acutely disturbed patient.

Schizophrenia is characterized by; delusions (paranoid), hallucinations, thought disorders and abnormal behavior, social withdrawal and flat emotions

Schizophrenia was found to be associated with increase in dopamine activity in the brain, with possible role for 5HT, so drug useful in this disease are expected to modify these neurotransmitters

A. Classification of antipsychotic drugs:

1. phenothiazines: chlorpromazine, promazine, promethazine, thioridazine, trifluperazine, prochlorperazine and fluphenazine
2. butyrophenones: haloperidol, benperidol
3. thioxanthines: flupentixol, zuclopenthioxol
4. atypical antipsychotic drugs: pimozide, loxapine

B. Mechanism of action:

- Antipsychotic drugs act by blocking dopamine D_2 receptors centrally in the brain, this blockade produces the antipsychotic and antiemetic effects.
- The antipsychotics also inhibit the function of the hypothalamus, which cause loss of temperature control, galactorrhea, amenorrhea, and weight loss
- The blockade of D_2 receptors also produces the extra-pyramidal symptoms

- The anti-psychotics can also act on other receptors which include:
  alpha adrenoceptor blockade
  anti-muscarinic
  histamine-H 1 receptor blockade
  serotonin (5HT) receptor blockade

C. Drugs

1. Phenothiazines

Chlorpromazine is the prototype of this group

Mechanism of action: They have central calming effect which inhibits hallucination (D2-blockade). They can also inhibit the chemoreceptor trigger zone and the hypothalamic function. They produce powerful extra-pyramidal effects. They have also alpha-adrenoceptor blockade, this causes postural hypotension

Pharmacokinetics:

Phenothiazines have variable absorption from the gastrointestinal tract with bioavailability of only 30%. The absorption is delayed by the presence of food. Peak plasma level is reached in 2-3 hours with half-life between 2 -24 hours. They are highly lipid soluble with a wide volume of distribution. They are mainly metabolized by the liver with large number of active metabolites. Phenothiazines are highly protein bound (90-95%).

Clinical uses of phenothiazines (chlorpromazine):

a. as anti-psychotic in schizophrenia especially useful in acute episodes
b. hypomania
c. severe anxiety not responding to benzodiazepines and panic state
d. co-analgesic in chronic pain and terminal illness

e. anti-emetic, due to inhibition of CTZ useful in vomiting due to metabolic disturbances, cytotoxic drugs and radiations
f. intractable hiccup due to phrenic nerve irritation
g. allergic conditions as promethazine has a strong antihistamine effect
h. in the treatment of non-pyrogen induced fever to lower body temperature

Adverse effects of phenothiazines:

1. Anticholinergic effects; blurred vision, dry mouth, constipation and urinary retention
2. Postural hypotension due to blockade of α_1 adrenoceptors
3. Excessive sedation, drowsiness , confusion and seizures
4. Abnormal involuntary movements including tremor, dystonia and dyskinesia, this is due to blockade of dopamine effect in the brain
5. Cholestatic jaundice occurs in 2-6% of patients as an idiosyncratic reaction
6. Allergic reactions; skin rash and bone marrow suppression
7. Cardio-toxicity; cardiac arrhythmias and conduction block
8. Interaction with other drugs:
    a. can potentiate the effect of other CNS depressant drugs
    b. anti-cholinergic effect decreases the absorption of other drugs
    c. potentiate the effect of anti-hypertensive drugs
    d. they can inhibit hepatic drug metabolizing enzymes and increase the toxicity of other drugs.

2. Butyrophenones:

Haloperidol:

It is used as alternative to phenothiazine as anti-psychotic drug . It has better bioavailability of about 60%, metabolized by the liver and has no pharmacologically active metabolites. Haloperidol causes less severe hypotension than phenothiazines, however it can cause extra-pyramidal symptoms like phenothiazines. Haloperidol can also cause leukopenia, agranulocytosis and jaundice

3. Atypical antipsychotic drugs:

Clozapine Olanzapine Resperidone

- Have similar mechanism of action to other drugs
- Cause few extra-pyramidal symptoms
- Allergic skin reactions are less common
- Clozapine is useful in schizophrenia resistant to other drugs

4. Depot preparation of antipsychotic drugs

Haloperidol Flupentixol

- Long acting form of the drug
- Contains fatty ester of the drug, which releases the drug slowly by the action of tissue esterase enzyme
- Is given every 4 weeks. It improves the patient compliance with treatment

Neuroleptic malignant syndrome

This syndrome may develop in up to 1% of patients taking antipsychotic drugs and is more common with high doses, especially in the elderly patients. Features include:

- Fever
- Confusion
- Rigidity of muscles

- Tachycardia
- Elevation of blood pressure
- Urinary retention