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MAJOR TRANQUILIZERS (NEUROLEPTICS)

I- Definition

Psycholeptics and thymoleptics, major sedatives used in the treatment of psychosis (schizophrenia, paranoia, autism, and manic-depressive psychosis). They act on **positive symptoms and negative symptoms**.

II- Classification

According to chemical structure

A-1 First-generation neuroleptics (Typical)

- Act mainly on **positive symptoms**
- Many side effects (+++)

1. **Phenothiazines**
   Tricyclic homogeneous structure

- Chlorpromazine (Largactil®)
- Levomepromazine (Nozinan®)

2. **Thioxanthenes**
   Tricyclic structure similar to phenothiazines, nitrogen replaced by carbon

- Flupentixol (Fluanxol®)
- Zuclopenthixol (Clopixol®)

3. **Butyrophenones**
   Derived from amino-4 fluorobutyrophenone

- Haloperidol (Haldol®)
- Droperidol (Droleptan®)

4. **Benzamides**
   Benzene ring linked by an amide bond with a side chain

- Metoclopramide (Primperan®)
- Sulpiride

A-2 Second-generation neuroleptics (Atypical)

- Act on **negative symptoms**
- Fewer side effects

1. **Dibenzodiazepines**

- Clozapine, Olanzapine, Quetiapine

2. **Benzisoxazoles**

- Risperidone

3. **Imidazolidinones**

- Sertindole

A-3 Long-acting neuroleptics (Depot forms)

Modified to alter pharmacokinetics and allow spaced administration

- **Prodrug forms**: gradual release after IM injection
  Example: Haloperidol decanoate
- **Polymer-based forms**: slow degradation in aqueous solution
  Example: Long-acting Risperidone (Risperdal Consta®)

According to clinical effects

- Sedative at low dose, antiproductive at high dose: Levomepromazine
- Antideficit at low dose, antiproductive at high dose, sedative at very high dose: Sulpiride
- Sedative and antiproductive without antideficit effect: Haloperidol

III- Pharmacokinetics

Absorption

- Oral: intestinal, variable (depends on lipophilicity, protein binding, degradation)
- IM: faster, complete in 3–4 hours (>90% bioavailability)
- IV: used in anesthesiology

Distribution

- Variable plasma protein binding
- Large volume of distribution (5–20 L/kg)
- High affinity for adipose tissue → prolonged storage
- Cross BBB, placenta, and breast milk

Metabolism

- Hepatic metabolism (CYP450)
- First-pass effect + intestinal metabolism → low bioavailability
- Multiple metabolites (active, inactive, or toxic)

Elimination

- Half-life generally >24 hours
- Renal elimination (main), biliary (secondary)
- Enterohepatic cycle may occur

IV- Mechanism of Action

Schizophrenia is due to dopamine imbalance:

- Excess in **mesolimbic pathway** → positive symptoms
- Deficit in **mesocortical pathway** → negative symptoms

a) Dopamine receptor antagonism

- Therapeutic and adverse effects

Pathways:

- Mesolimbic → desired effect
- Mesocortical → worsens negative symptoms
- Nigrostriatal → extrapyramidal syndrome (Parkinson-like)
- Tuberoinfundibular → hyperprolactinemia

b) Serotonin (5-HT2) antagonism

- Reduces D2 receptor occupancy → fewer side effects

c) Muscarinic antagonism

- Peripheral: dry mouth, constipation, visual disturbances
- Central: sedation, memory impairment

d) Alpha-1 adrenergic antagonism

- Orthostatic hypotension
- Sedation
- Sexual dysfunction

e) Histamine receptor antagonism

- Increased appetite → weight gain
- Decreased alertness

V- Side Effects

- Sedation, drowsiness, anxiety, depression
- Acute or tardive dyskinesia
- Extrapyramidal syndrome
- Akathisia
- Anticholinergic effects (dry mouth, constipation, urinary retention)
- Cardiovascular effects (hypotension, arrhythmias)
- Hormonal disorders (amenorrhea, gynecomastia, impotence)
- Metabolic disorders

Severe adverse effects

- **Agranulocytosis (especially Clozapine)**
- **Neuroleptic malignant syndrome (NMS)**
    - Hyperthermia (40–42°C)
    - Muscle rigidity
    - Rhabdomyolysis
    - Renal failure
    - Altered consciousness

Management :

- Stop treatment
- Cooling + hydration
- Dopaminergic drugs (Levodopa, Bromocriptine)
- Intensive care

V- Contraindications

- Hypersensitivity
- Parkinson's disease
- Angle-closure glaucoma
- Elderly patients

VI- Drug Interactions

- Alcohol → increased sedation
- Dopamine agonists (Levodopa) → antagonism
- Clozapine + Carbamazepine → hematological risk

VII- Acute Toxicity

Low therapeutic index

Typical neuroleptics

- Coma
- Extrapyramidal syndrome
- Respiratory depression
- Cardiac disorders (QT prolongation, torsades de pointes)
- Dystonia

Atypical neuroleptics

- Clozapine → agranulocytosis risk
- Olanzapine → sedation, hypotension, respiratory depression

VIII- Treatment

Mainly **symptomatic treatment**

IX- Analysis

- Samples: blood, urine, gastric lavage
- Low blood concentrations

Methods:

1. Colorimetric reactions
2. Thin-layer chromatography
3. Liquid chromatography