

## Pharmacology of CNS Drugs

### BASIC PHARMACOLOGY OF SEDATIVE-HYPNOTICS

Anxiety states and sleep disorders are common problems,

An effective **sedative** (anxiolytic) agent should reduce anxiety and exert a calming effect. A **hypnotic** drug should produce drowsiness and sleep.

Hypnotic effects involve more depression of the central nervous system than sedation, and this can be achieved with many drugs.

The benzodiazepines are widely used sedative-hypnotics. other Barbiturate, Meprobamatees.

### MOA of Benzodiazepines, Barbiturates, Newer Hypnotics

The BZ, the barbiturates, , and other drugs bind to molecular components of the GABA receptor in neuronal membranes in the CNS.

BZ potentiate GABAergic inhibition at all levels of the neuron axis,

**Tolerance** decreased responsiveness to drug following repeated exposure is a common feature of sedative-hypnotic use.

### ORGAN LEVEL EFFECTS

**1. Sedation**

**2. Hypnosis**

**3. Anesthesia**

**4. Anticonvulsant effects**

**5. Muscle relaxation**

**6- Effects on respiration and cardiovascular function at**

## **CLINICAL PHARMACOLOGY OF SEDATIVE-HYPNOTICS**

- 1-Relief of anxiety Insomnia,
- 2- Sedation and amnesia before and during surgical procedures
- 3- Diagnostic aids or for treatment in psychiatry
- 4- Treatment of epilepsy and seizure states
- 5- Component of balanced anesthesia (intravenous administration)
- 6- Control of ethanol or other sedative-hypnotic withdrawal states
- 7- Muscle relaxation in specific neuromuscular disorders

### **Adverse effects of sedative-hypnotics**

Drowsiness, impaired judgment, and diminished motor skills, sometimes with a significant impact on driving ability, job performance, and personal relationships.

Benzodiazepines may cause a significant dose-related amnesia; they can significantly impair ability to learn new information, particularly that involving cognitive processes

### **Barbiturates**

#### **Uses of barbiturates:**

limited to intractable insomnia in patients already taking barbiturates (should be avoided in the elderly). used for epilepsy, thiopental for anaesthesia.

#### **Overdose of barbiturates**

hypothermia, respiratory depression and coma

.

## Nonbenzodiazepine hypnotics

Although structurally unrelated to the benzodiazepines, these drugs act on the same receptor complex but at different sites from BZ

**Zopiclone      Zolpidem      Zaleplon**

### **Chloral hydrate**

has a fast (30-60 min) onset of action and duration of action 6-8 h. It is a prodrug, being rapidly metabolised by alcohol dehydrogenase into the active hypnotic trichloroethanol (t<sub>1/2</sub> 8h is dangerous in serious hepatic or renal failure and aggravates peptic ulcer

## PHARMACOLOGY OF ANTISEIZURE DRUGS

**Epilepsy** is a complex chronic disorder characterized by recurrent seizures. Seizures are finite episodes of brain dysfunction resulting from abnormal discharge of cerebral neurons. The causes of seizures include the full range of neurologic diseases, from infection to neoplasm and head injury. In some subgroups, inheritance has a predominant factor

The classic major drugs for partial and generalized tonic-clonic seizures are **phenytoin, carbamazepine, valproate**, and the **barbiturates**.

newer drugs **lamotrigine, levetiracetam, gabapentin, oxcarbazepine, pregabalin, topiramate, vigabatrin**, and **zonisamide**

## Antidepressant Agents

Major depression is one of the most common psychiatric disorders. At any given moment, about 3-5% of the population is depressed and an estimated 10% of people may become depressed during their lives. The symptoms of depression are often unrecognized both by patients

and by physicians. A variety of chemical structures have been found to have antidepressant activity.

### **A. TRICYCLIC ANTIDEPRESSANTS (TCAS)**

Tricyclic antidepressants- have been used clinically for four decades. **Imipramine** and **amitriptyline** are the prototypical drugs of the class as mixed norepinephrine and serotonin uptake inhibitors, although they also have several other effects.

### **B. SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)**

**fluoxetine**-an effective and more selective antidepressant with minimal autonomic toxicity.

### **C. MONOAMINE OXIDASE (MAO) INHIBITORS**

**phenelzine** and **isocarboxazid** (no longer marketed); or Tranylcypromine which is itself a weak inhibitor of MAO.

## **CLINICAL PHARMACOLOGY OF ANTIDEPRESSANTS**

- A. Depression
- B. Anxiety disorders ,panic ,generalized anxiety ,social phobia
- C. Chronic pain
- D. Enuresis.

## **ALCOHOLS**

Ethanol is a small molecule that is absorbed rapidly from the gastrointestinal tract. After ingestion of alcohol in the fasting state, peak blood alcohol concentrations are reached within 30 minutes. The presence of food in the gut delays absorption by slowing gastric emptying,. women have a higher peak concentration than men, in part because women have a lower total body water content.

### **EFFECT OF ALCOHOLS**

Alcohol causes sedation and slurred speech, ataxia, impaired judgment, induces coma, respiratory depression, and death., Significant depression of myocardial contractility has been observed in individuals who acutely consume moderate amounts of alcohol

## **Consequences of Chronic Alcohol Consumption**

### **A. LIVER AND GASTROINTESTINAL TRACT**

Chronic alcohol ingestion is the most common cause of Liver disease, chronic pancreatitis. gastritis. injures the small intestine.

### **B. NERVOUS SYSTEM**

The consumption of alcohol results in tolerance and in physical and psychological dependence(need to repeated drug intake). Consumption of large amounts of alcohol leads to neurologic deficits. generalized symmetric peripheral nerve injury, disturbances and ataxia that are due to degenerative changes in the central nervous system. dementia, ataxia, and a confused state that can progress to coma and death.

### **C. CARDIOVASCULAR SYSTEM**

Cardiomyopathy, heart failure, Arrhythmias, Hypertension, Coronary heart disease

### **D. FETAL ALCOHOL SYNDROME**

Ethanol rapidly crosses the placenta and reaches concentrations in the fetus that are similar to those in maternal blood. Chronic maternal alcohol drink during pregnancy is associated with teratogenic effects, and alcohol appears to be a leading cause of mental retardation and congenital malformation.

### **E .INCREASED RISK OF CANCER**

Chronic alcohol drink increas the risk of cancer of the mouth, pharynx, larynx, esophagus, and liver

## Central Nervous System Stimulants

Many drugs stimulate the CNS, but only a few are used therapeutically, and their indications for use are limited. Two disorders treated with CNS stimulants (Narcolepsy, Attention Deficit-Hyperactivity Disorder ADHD)

### TYPES OF STIMULANTS

**Amphetamines, Amphetamine-related drug (methylphenidate)**

**Xanthenes'**

## PAIN

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, also can occur without tissue injury or evident disease and can persist after injury has healed. (Mild pain, Moderate pain, Severe pain, Overwhelming acute pain)

### TYPES OF PAIN

Acute pain

Transient pain

Neuropathic

Chronic pain

Acute and transient pain is managed primarily by analgesic drugs.

Chronic and neuropathic pain often requires analgesic drugs and adjuvant drugs as well as non drug measures.

#### **Analgesic drug:**

a drug that relieves pain due to multiple causes, e.g. paracetamol, morphine., Analgesics are chosen according to the cause of pain and its severity..

#### **Adjuvant drugs**

are those used alongside analgesics in the management of pain.

- **Analgesics** are classed as

### **Narcotic**

(which act in the central nervous system and cause drowsiness, i.e. opioids) and

### **Non-Narcotic**

(which act chiefly peripherally, e.g. diclofenac).

### **Narcotic or opioid analgesics**

#### **The principal actions of morphine:**

##### 1-CNS:

- Depression:
- Excitation,
- Changes of mood:
- Dependence;

2-Peripheral nervous system: Analgesia, some anti-inflammatory effect

##### 3-Smooth muscle stimulation:

- GI muscle spasm (delayed passage of contents with constipation)
- Biliary tract spasm
- Bronchospasm

4-Cardiovascular system :Dilatation of (arterioles) and (veins) vessels.

#### **PRINCIPAL USES OF MORPHINE AND ITS ANALOGUES**

- Relief of moderate to severe acute pain
- Premedication ,postoperative analgesia for surgery
- Symptomatic control of acute diarrhea, e.g. travelers" diarrhea (codeine)
- Suppression of cough (codeine)
- Production of euphoria as well as pain relief in the dying.

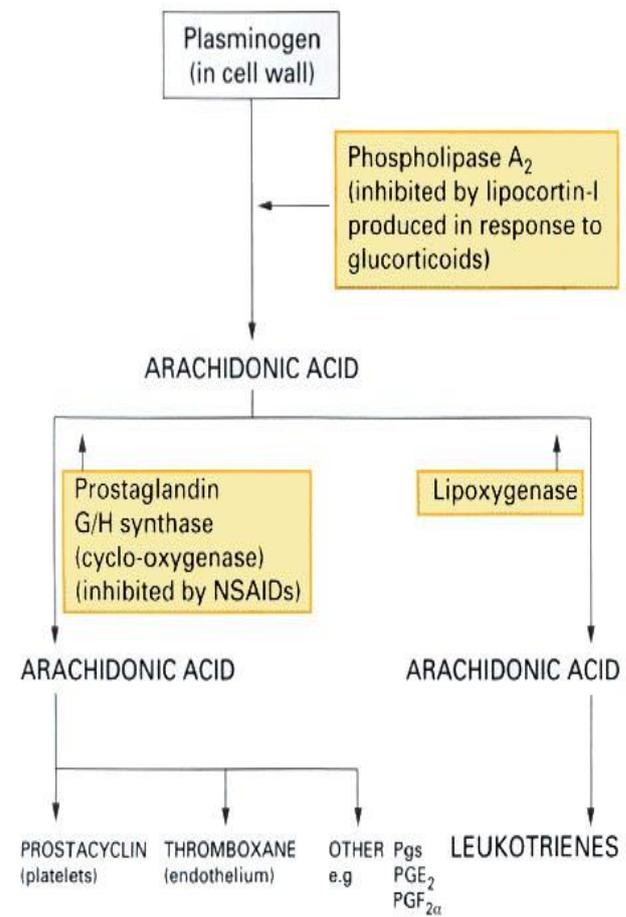
## Nonsteroidal anti-inflammatory drugs (NSAIDs)

### Non Steroidal Anti-Inflammatory Drugs (NSAIDs)

#### MODE OF ACTION

The members of this class of drug, although structurally heterogeneous, possess a mode of action which is to *block prostaglandin synthesis* ,, their key action of inhibiting prostaglandin formation is reflected in the range of effects, beneficial and adverse, which the members exhibit. NSAIDs may be categorized according to their COX specificity as:

- COX-2 *selective* compounds, for inhibiting COX-2 is at least 5 times that for COX- 1.( **Rofecoxib, Celecoxib Meloxicam, Nabumetone**).
- *Non- selective* compounds, which comprise all other NSAIDs. These drugs inhibit COX-1 as much as, or even more than, COX-2.



## USES

- .1- Analgesia:
- 2-Anti-inflammatory action:
- 3-Antipyretic action:
- 4-Antiplatelet function:
- 5-Prolongation of gestation and labour:
- 6-Primary dysmenorrhoea:

## ADVERSE REACTIONS

**Gastrointestinal effects** Gastric and intestinal mucosal damage is the commonest adverse effect of NSAIDs. Indigestion, gastro-oesophageal reflux, erosions, peptic ulcer,

Clinical trial evidence in general appears to support the theory that COX-2 selective inhibitors are as effective as, but have fewer adverse effects than, non-COX-2 selective compounds; for example meloxicam is better tolerated than diclofenac or piroxicam

### **Renal effects**

Renal blood flow is reduced ,there salt sodium and fluid retention and arterial blood pressure may rise.

**Other general effects** include cholestasis, hepatocellular toxicity, haemolytic anemia. Urticaria, severe rhinitis and asthma occur in susceptible individuals, e.g. with exposed to NSAIDs, notably aspirin; the mechanism may involve inhibition of synthesis of bronchodilator prostaglandins, Other effects on the skin include photosensitivity, erythema multiforme, urticaria,

## ANESTHESIA

### GENERAL ANESTHESIA

General anesthesia is a state of (CNS) depression, during which there is complete loss of sensation, consciousness, pain perception, and memory. It has three components: **hypnosis, analgesia, and muscle relaxation**

Several different drugs are usually combined to produce desired levels of these components without excessive CNS depression. This so-called **Balanced surgical anesthesia (hypnosis with analgesia and muscular relaxation)** also allows lower dosages of potent general anesthetics.

### STAGES OF GENERAL ANAESTHESIA

Surgical anesthesia is classically divided into four stages: **Analgesia, Excitement, Surgical anesthesia and Medullary paralysis (overdose).**

### ADJUFANT TO ANESTHESIA

Several non anesthetic drugs are used as adjuncts to anesthetic drugs. include **antianxiety , sedative-hypnotics , anticholinergics, and opioid analgesics, neuromuscular blocking agents.**

**Before surgery (premedication)**

**Anxiolysis and amnesia.** . Sedative premedication

Benzodiazepines, provide anxiolysis and amnesia for the immediate presurgical period

**Analgesia** is indicated if the patient is in pain preoperatively or it can be given to prevent postoperative pain

**Drying of bronchial and salivary secretions** using antimuscarinic drugs .the antimuscarinic of choice for this purpose atropine and hyoscine

**After surgery**

Relief of pain

opioid provides excellent pain relief after major surgery such as laparotomy.

like Parenteral morphine, The addition of regular paracetamol and a NSAID, will provide additional pain relief and reduce the requirement for morphine. NSAIDs are contraindicated if there is a history of gastrointestinal ulceration , renal blood flow is compromised

**During surgery**

The aim is to induce unconsciousness, analgesia and muscular relaxation. A typical general anesthetic consists of:

**Induction:****• Maintenance:**

**Inhalation anaesthetics**

, **nitrous oxide** and the fluorinated hydrocarbonse

**Halothane, Isoflurane , Sevoflurane, Enflurane ,. Desflurane)**

**Intravenous anaesthetics**

**Propofol , Thiopental, Etomidate, Ketamine**

**Local Anesthesia**

reversible loss of sensation in a limited area of the body caused by a depression of excitation in nerve ending or an inhibition of the conduction process in peripheral nerve

**Mechanism of Action**

The primary mechanism of action of local anesthetic is blockade voltage gated sodium channels.

**Clinical Effect and uses of Lidocaine**

1.Local anesthetic effect

2.Cardiovascular effect lidocaine decrease electrical excitability of the myocardium, decrease conduction rate and decrease force of contraction

3. Central Nervous System effect

A: Anticonvulsant effect

B: increase pain threshold and may produce degree of analgesia

.

**Vasoconstrictors**

. are the agents add to local anesthetic solutions to oppose vasodilatation and achieve hemostasis.