Shree H.N.Shukla institute of Pharmaceutical Education & Research Rajkot

B.Pharm

Semester IV

Subject Name: Pharmacology I
Subject code:BP404TP

TOPIC:

a. Neurohumoral transmission in the C.N.S.special emphasis on importance of various neurotransmitters like with GABA, Glutamate, Glycine, serotonin, dopamine.

b. General anesthetics and pre-anesthetics.

c. Sedatives, hypnotics and centrally acting muscle relaxants.

d. Anti-epileptics

e. Alcohols and disulfiram

a. Psychopharmacological agents: Antipsychotics, antidepressants, anti-anxiety agents, anti-manics and hallucinogens.

b. Drugs used in Parkinsons disease and Alzheimer's disease.

c. CNS stimulants and nootropics.

d. Opioid analgesics and antagonists

e. Drug addiction, drug abuse, tolerance and dependence.

NEUROTRANSMITTERS IN CNS

Neurotransmitters in the central nervous system (CNS) could be inhibitory, excitatory or both

1. Inhibitory neurotransmitters
   - GABA
   - Glycine
   - Dopamine

   → CNS⊖ → Inhibitory effect on CNS

2. Excitatory neurotransmitters
   - Glutamate
   - Aspartate

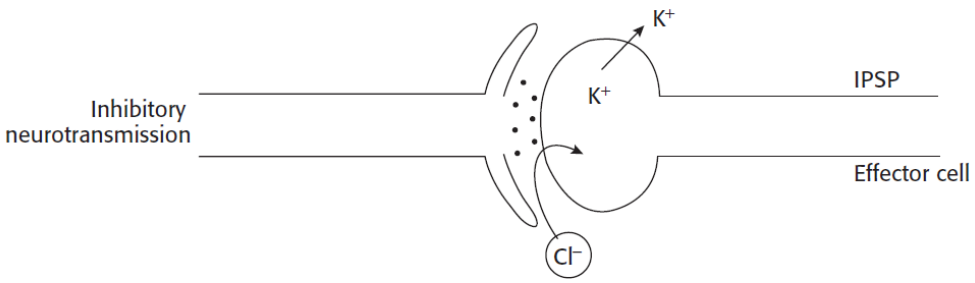
   → CNS⊕ → Stimulatory effect on CNS

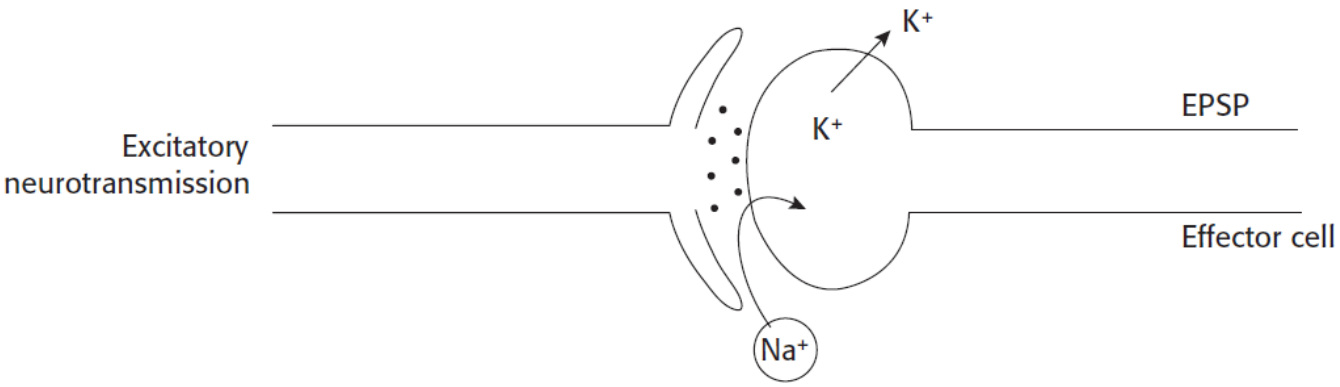
3.
   - Acetylcholine
   - Noradrenaline
   - Serotonin (5-HT)

   → Mediate both inhibitory and excitatory effects

Inhibitory Postsynaptic Potential (IPSP)

When an inhibitory transmitter binds and interacts with specific receptors on postjunctional membrane, the membrane permeability to K" or Cl# increases.





Excitatory Postsynaptic Potential (EPSP)

When an excitatory neurotransmitter binds and interacts with specific receptors on postjunctional membrane, the membrane permeability to cations increases.

SEDATIVES AND HYPNOTICS

Sedative is a drug that reduces excitement and calms the person. Hypnotic is a drug that produces sleep-resembling normal sleep.

SLEEP

The phases of sleep include nonrapid eye movement (NREM) sleep and rapid eye movement(REM) sleep. NREM sleep is divided into the following stages: 0, 1, 2, 3 and 4. Normally, about 50% of sleep time is spent in stage 2. Slow wave sleep includes stages 3 and 4. REM sleep constitutes about 30% of the sleep time and lasts for 5–30 minutes in each cycle of sleep.

CLASSIFICATION OF SEDATIVES AND HYPNOTICS

1.**Benzodiazepines (BZDs)**: Diazepam, lorazepam, clonazepam, clobazam, chlordiazepoxide, oxazepam, temazepam, midazolam, alprazolam, triazolam, flurazepam, nitrazepam.

Table 5.1 ■ **Types of sleep disorder and their treatment**

Sleep disorder	Treatment
Lack of sleep (insomnia) • Transient insomnia (<3 days) • Short-term insomnia (3 days–3 weeks) • Long-term insomnia (>3 weeks)	Sedatives and hypnotics
Hypersomnia (narcolepsy)	Amphetamine, modafinil, amitriptyline
Nocturnal enuresis (bed wetting)	Tricyclic antidepressants

2. **Barbiturates**:

Long acting: Phenobarbitone

Short acting: Pentobarbitone

Ultrashort acting: Thiopentone, methohexitone

3. **Nonbenzodiazepine hypnotics**: Zolpidem, zopiclone, zaleplon, eszopiclone

4. **Others**: Melatonin, ramelteon suvorexant

BENZODIAZEPINES

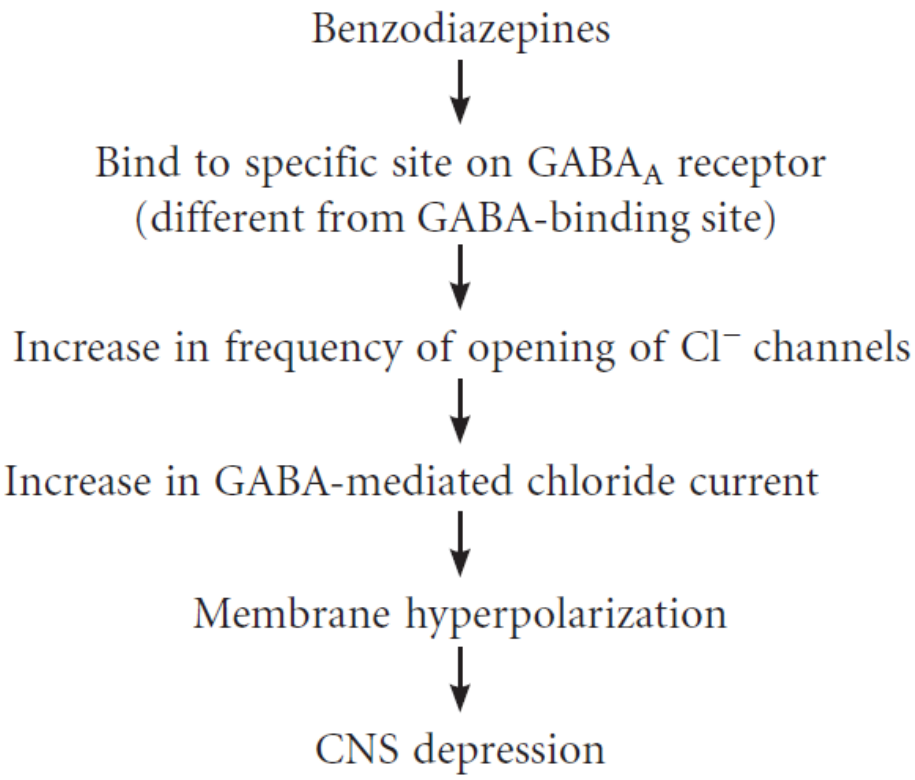
All BZDs have a benzene ring fused to a seven-membered diazepine ring.

Sites of Action

Midbrain (ascending reticular formation), limbic system, brain stem, etc.

Mechanism of Action

BZDs facilitate action of GABA – they potentiate inhibitory effects of GABA.



BZDs have no GABA-mimetic action.

Pharmacological Actions and Therapeutic Uses

1. Sedation and hypnosis: BZDs decrease time required to fall asleep (sleep latency). The total sleep time is increased. They shorten all stages of NREM sleep except stage 2, which is prolonged. The duration of REM sleep is usually decreased. BZDs reduce night awakenings and produce refreshing sleep. At present, BZDs are preferred to barbiturates for treatment of short-term insomnia because:

They have a wide therapeutic index.

They cause near-normal sleep; less rebound phenomena on withdrawal.

They produce minimal hangover effects (headache and residual drowsiness on waking).

They cause minimal respiratory depression.

They are less likely to cause tolerance and dependence when used for short period.

They have no enzyme-inducing property; hence, drug interactions are less.

They have a specific BZD-receptor antagonist, flumazenil, for the treatment of overdosage.

Long-term use of BZDs for insomnia is not recommended because of development of tolerance, dependence and hangover effects; but these drugs are ideal for occasional use by air travellers, shift workers, etc.

2. Anticonvulsant: Diazepam, lorazepam, clonazepam, clobazam, etc. have anticonvulsant effect. Intravenous (i.v.) diazepam/lorazepam is used to control life-threatening seizures in status epilepticus, tetanus, drug-induced convulsions, febrile convulsions, etc. Clonazepam is used in the treatment of absence seizures.

3. Diagnostic (endoscopies) and minor operative procedures: i.v. BZDs are used because of their sedative–amnesic–analgesic and muscle relaxant properties.

4. Preanaesthetic medication and general anaesthesia (GA): These drugs are used as preanaesthetic medication because of their sedative–amnesic and anxiolytic effects.

Hence, the patient cannot recall the perioperative events later. i.v. diazepam, lorazepam, midazolam, etc. are combined with other CNS depressants to produce GA.

5. Antianxiety (anxiolytic) effect: Some of the BZDs (diazepam, oxazepam, alprazolam, lorazepam, chlordiazepoxide, etc.) have selective antianxiety action at low doses. The anxiolytic effect is due to their action on limbic system. Tolerance to antianxiety action of BZDs develops only on prolonged use.

6. Muscle relaxant (centrally acting): They reduce skeletal muscle tone by inhibiting polysynaptic reflexes in the spinal cord. The relaxant effect of BZDs is useful in spinal injuries, tetanus, cerebral palsy and to reduce spasm due to joint injury or sprain.

7. To treat alcohol-withdrawal symptoms: Long-acting BZDs, such as chlordiazepoxide and diazepam are used.

Pharmacokinetics

BZDs are usually given orally or intravenously and occasionally by rectal route (diazepam) in children. The rate of absorption following oral administration is variable; absorption is erratic from intramuscular (i.m.) site of administration; hence rarely used. They have a large volume of distribution. They have a short duration of action on occasional use because of rapid redistribution, hence, are free of residual (hangover) effects, even though elimination half-life is long. BZDs are metabolized in liver. Some undergo enterohepatic recycling. Some of them produce active metabolites which have long half-life; hence, cumulative effects may be seen. Oxazepam is not significantly metabolized in liver. The metabolites are excreted in urine. BZDs cross placental barrier.

Adverse Effects

BZDs have a wide margin of safety. They are generally well tolerated. The common side effects are drowsiness, confusion, blurred vision, amnesia, disorientation, tolerance and drug dependence. Withdrawal after chronic use causes symptoms like tremor, insomnia, restlessness, nervousness and loss of appetite. Use of BZDs during labour may cause respiratory depression and hypotonia in newborn (Floppy baby

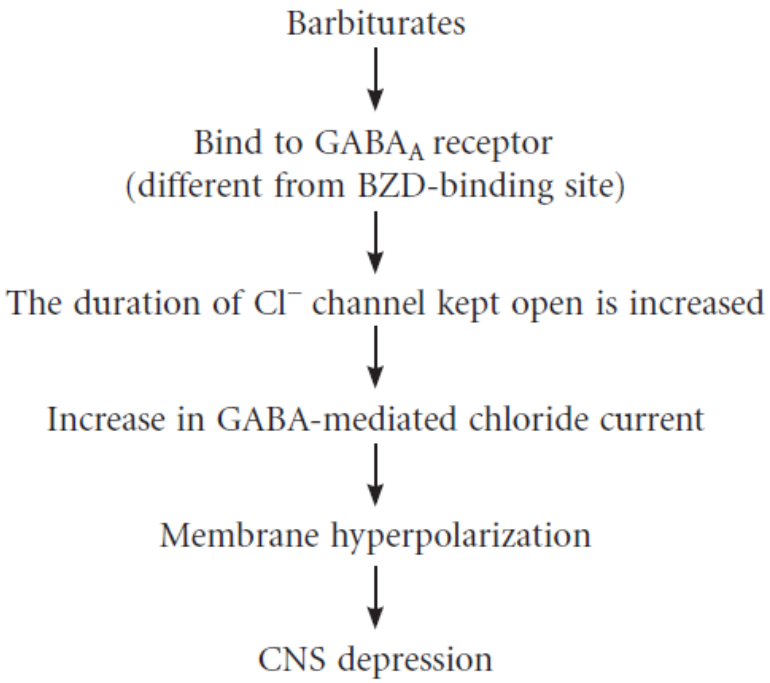
syndrome). In some patients, these drugs may produce paradoxical effects, i.e. convulsions and anxiety.

BARBITURATES

All barbiturates are derivatives of barbituric acid. They are nonselective CNS depressants and act at many sites, ascending reticular activating system (ARAS) being the main site.

Mechanism of Action

Barbiturates have GABA facilitatory action – they potentiate inhibitory effects of GABA.



At high concentrations, barbiturates have **GABA-mimetic effect** (i.e. barbiturates can directly increase Cl^- conductance into the neuron).

Pharmacological Actions and Uses

1. Sedation and hypnosis: Barbiturates were used in the treatment of insomnia.

They decrease sleep latency, duration of REM sleep, stage 3 and 4 of NREM sleep.

They cause marked alteration of sleep architecture. At present, barbiturates are

not recommended because:

They have a low therapeutic index.

They cause rebound increase in REM sleep on stoppage of therapy.

They cause marked respiratory depression.

They produce marked hangover effects (headache and drowsiness next day morning).

They cause high degree of tolerance and drug dependence.

They are potent enzyme inducers and cause many drug interactions.

They have no specific antidote.

2. General anaesthesia (GA): Ultrashort-acting barbiturates (thiopentone and methohexitone) may be used for induction of GA.

3. Anticonvulsant: Phenobarbitone has anticonvulsant effect and is used in the treatment of status epilepticus and generalized tonic–clonic seizures (GTCS, grand mal epilepsy).

4. Neonatal jaundice of nonhaemolytic type: Phenobarbitone may be used to reduce serum bilirubin levels. It induces glucuronyl transferase enzyme and hastens the metabolism of bilirubin.

Adverse Effects

1. The common side effects are drowsiness, confusion, headache, ataxia, hypotension and respiratory depression.

2. Hypersensitivity reactions like skin rashes, itching and swelling of face may occur.

3. Tolerance develops to their sedative and hypnotic actions on repeated use.

4. Physical and psychological dependence develops on repeated use.

5. Prolonged use of phenobarbitone may cause megaloblastic anaemia by interfering with absorption of folic acid from gut.

6. They may precipitate attacks of acute intermittent porphyria by inducing ALA synthase that catalyses the production of porphyrins; hence, barbiturates are contraindicated in porphyria.

7. Acute barbiturate poisoning: The signs and symptoms are drowsiness, restlessness, hallucinations, hypotension, respiratory depression, convulsions, coma and death.

Treatment of acute barbiturate poisoning

Maintain airway, breathing and circulation.

Maintain electrolyte balance.

Gastric lavage – after stomach wash, administer activated charcoal that may enhance the elimination of phenobarbitone. Endotracheal intubation is performed before gastric lavage to protect the airway in unconscious patients.

Alkaline diuresis – there is no specific antidote for barbiturates; main treatment is alkaline diuresis. i.v. $NaHCO_3$ alkalinizes urine. Barbiturates are weakly acidic drugs. In alkaline urine, barbiturates exist in ionized form, so they are not reabsorbed while passing through renal tubules and are rapidly excreted in urine. Haemodialysis is employed in severe cases.

Drug Interactions

Barbiturates are potent inducers of hepatic microsomal enzymes and reduce the effectiveness of co-administered drugs (e.g. oral contraceptives [OCs], oral anticoagulantsand oral hypoglycaemics).

Nonbenzodiazepine Hypnotics

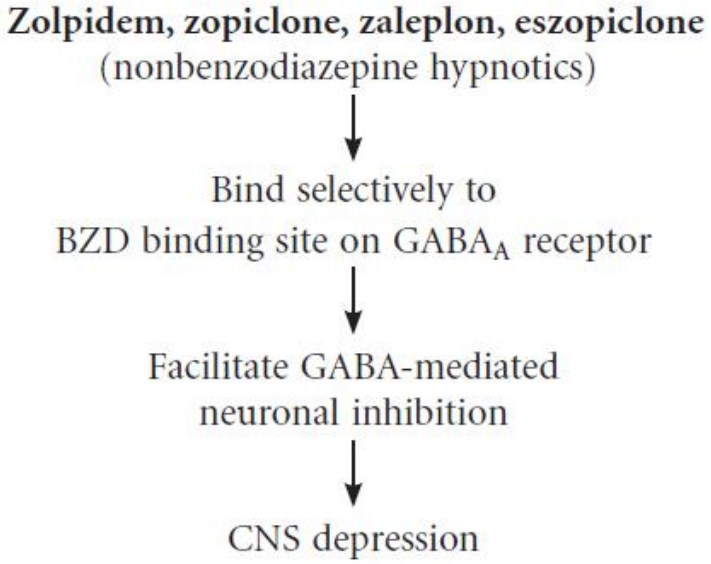
They include zolpidem, zopiclone, zaleplon, eszopiclone and etizolam. They have less

potential for abuse than BZDs. They have less antianxiety, anticonvulsant and muscle relaxant effects than BZDs. Effect on REM sleep is less as compared to BZDs.

ZOLPIDEM

Zolpidem mainly produces hypnotic effect – decreases sleep latency and increases duration of sleep time in insomnia. It produces near-normal sleep like BZDs with minimal alteration in REM sleep; causes minimal hangover effects and rebound insomnia; less likely to produce tolerance and drug dependence; lacks anticonvulsant, antianxiety and muscle relaxant effects. It is given orally, well absorbed, metabolized in liver and excreted in urine. It has a short duration of action and is used for short-term treatment of insomnia. The actions of zolpidem are antagonized by flumazenil. The common side effects are headache, confusion, nausea and vomiting.

Mechanism of Action



ZOPICLONE

It is orally effective and is used for short-term treatment of insomnia. It produces nearnormal sleep like BZDs. The side effects are headache, drowsiness, GI disturbances and metallic taste.

ZALEPLON

It is useful in sleep onset insomnia. It is the shortest acting non-BZD hypnotic.

ESZOPICLONE

It is used orally for short- and long-term treatment of insomnia.

ETIZOLAM

It is a BZD analogue with hypnotic, anticonvulsant, muscle relaxant and antianxiety effects. It is useful for short-term treatment of insomnia.

MELATONIN

It is the hormone secreted by the pineal gland; involved in the maintenance of sleep–

wake cycle and circadian rhythm.

RAMELTEON

It is a melatonin-receptor (MT1 and MT2) agonist, can be used orally for the treatment of sleep onset insomnia. It reduces sleep latency and prolongs total duration of sleep. There is no rebound insomnia on withdrawal; does not cause tolerance on chronic use. The important adverse effects are fatigue and dizziness.

TASIMELTEON

It is another melatonin-receptor agonist used for the treatment of circadian rhythm disorder in blind patients.

SUVOREXANT

It prevents orexin from maintaining wakefulness by blocking orexin receptors. It is useful in chronic insomnia.

GENERAL ANAESTHETICS

GA refers to drug-induced reversible loss of consciousness and all sensations. The features of GA are as follows:

1. Reversible loss of consciousness.

2. Reversible loss of sensation.

3. Analgesia and amnesia.

4. Muscle relaxation and abolition of reflexes.

There is no single anaesthetic agent that can produce all the above effects. Hence, anaesthetic protocol includes:

1. Premedication.

2. Induction of anaesthesia (e.g. propofol).

3. Maintenance of anaesthesia (e.g. N2O " isoflurane).

4. Skeletal muscle relaxation.

5. Analgesia – as premedication, during and after the operation.

6. Use of other drugs:

To reverse neuromuscular blockade.

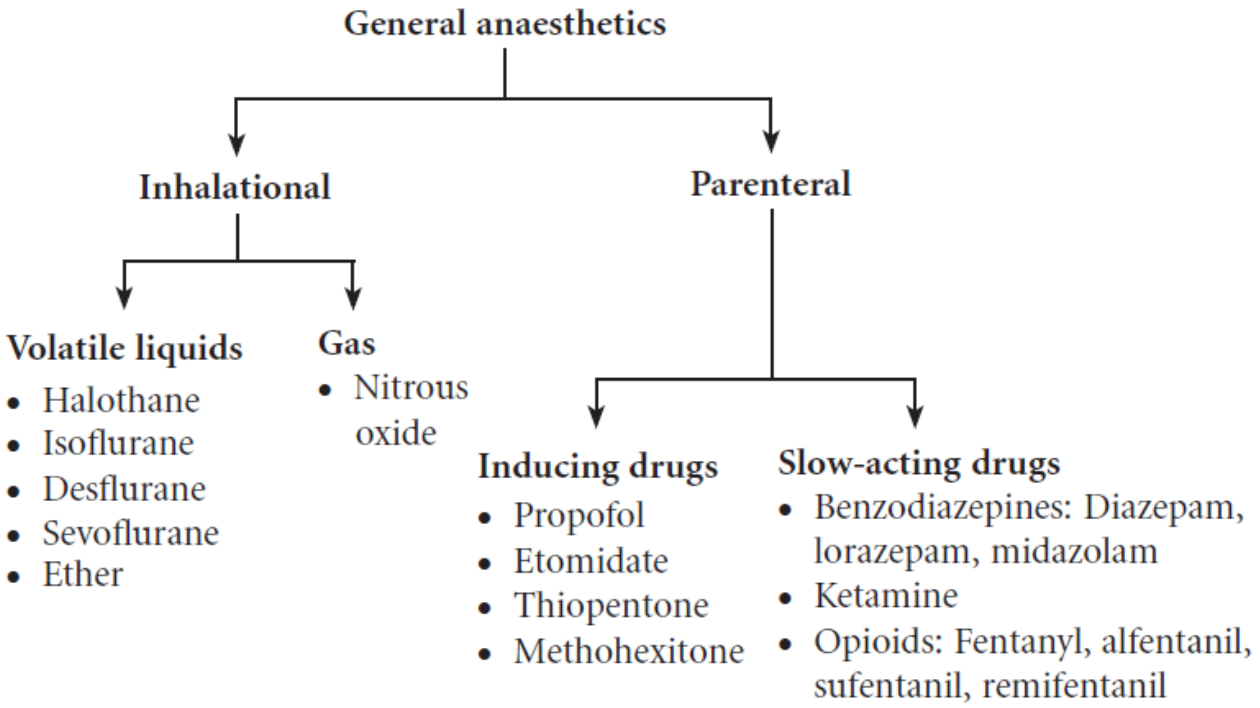
To reverse the residual effects of opioids (naloxone) and BZDs (flumazenil).

Minimal alveolar concentration (MAC) is the minimum concentration of an anaesthetic in alveoli required to produce immobility in response to a painful stimulus in 50% patients. It indicates the potency of inhalational general anaesthetics (N2O % 100%, halothane 0.75%).

Table 5.3 ■ **Stages of anaesthesia**

I. Stage of analgesia	II. Stage of excitement	III. Stage of surgical anaesthesia	IV. Stage of medullary paralysis
The patient is conscious but drowsy	• Patient loses consciousness • Sympathetic activity is increased • ↑ Heart rate (HR), ↑ blood pressure (BP), pupils are dilated; muscle tone is increased; breathing is irregular	• Respiration becomes regular • Muscles relax • Reflexes are gradually lost • Intercostal muscles are paralysed • Pupils dilated and eyeballs are fixed	Respiration and vasomotor centre are depressed; death occurs within a few minutes

CLASSIFICATION



COMPLICATIONS OF GENERAL ANAESTHESIA

CVS: Hypotension, cardiac arrhythmias, cardiac arrest

Respiratory depression, aspiration pneumonia, apnoea

CNS: Convulsions, persistent sedation

GIT: Nausea, vomiting, hepatotoxicity

Nephrotoxicity

Malignant hyperthermia

LOCAL ANAESTHETICS

Local anaesthetics (LAs) are drugs which, when applied topically or injected locally, block nerve conduction and cause reversible loss of all sensation in the part supplied

by the nerve. The order of blockade of nerve function proceeds in the following manner – pain, temperature, touch, pressure and finally skeletal muscle power.

CLASSIFICATION OF LOCAL ANAESTHETICS

1. According to clinical use

(a) Surface anaesthetics: Cocaine, lignocaine, tetracaine, benzocaine, oxethazaine, proparacaine, butylaminobenzoate.

(b) Injectable anaesthetics

(i) Short acting with low potency: Procaine, chloroprocaine.

(ii) Intermediate acting with intermediate potency: Lignocaine, mepivacaine, prilocaine, articaine.

(iii) Long acting with high potency: Tetracaine, bupivacaine, dibucaine, ropivacaine.

2. According to structure

(a) Esters*: Cocaine, procaine, chloroprocaine, benzocaine, tetracaine.

(b) Amides*: Lignocaine, mepivacaine, bupivacaine, prilocaine, articaine, ropivacaine.

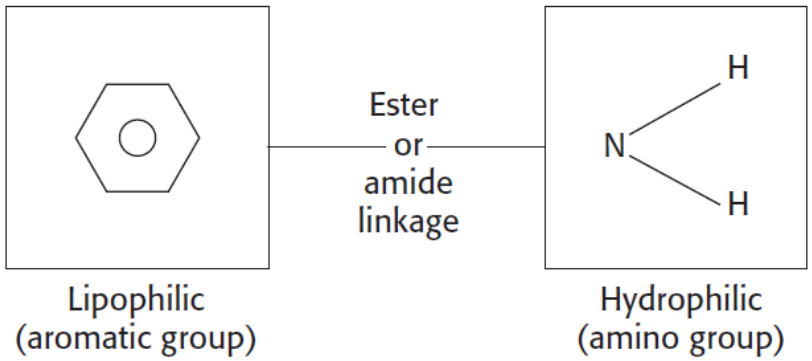


Fig. 5.6 Basic structure of local anaesthetics.

MECHANISM OF ACTION