UNIT-V

GENERAL ANESTHETICS

General anaesthetics are group of drugs that produces loss of consciousness, and therefore, loss of all sensations. The absolute loss of sensation is termed as anaesthesia. General anaesthetics bring about descending depression of the central nervous system (CNS), starting with the cerebral cortex, the basal ganglia, the cerebellum, and finally the spinal cord. These drugs are used in surgical operations to induce unconsciousness and, therefore, abolish the sensation of pain.

Stages of General Anesthesia: When an inhalation anesthetic is administered to a patient some of the following well defined stages are produced by increasing the blood concentration of the agent. They are;

Stage I (Stage of analgesia): This is the period from the beginning of anesthetic administration to the loss of consciousness. The patient progressively loses pain. This stage is also called stage of analgesia.

Stage II (Stage of delirium): This period extends from the loss of consciousness through a stage of irregular and specific breathing to the reestablishment of regular breathing. Respiration is normal and regular. The patient may laugh, vomit or struggle and for this reason it is called the stage of excitement.

Stage III (Stage of surgical anesthesia): In this stage excitement is lost and skeletal muscle relaxation is produced. Most types of surgeries are done in this stage.
Stage IV (Stage of medullary depression): Overdose of the anesthetic may bring the patient to this stage. Respiratory and circulatory failure occur in this stage.

Classification of GA

The general anesthetics are classified according to their nature (volatile or non-volatile) at room temperature. They are:

A. Volatile Inhalation general anesthetics. They are administered by inhalation and are further subdivided as;

1. Gases: Cyclopropane: Ethyl chloride, Nitrous oxide

2. Liquids: Diethyl ether, Halothane, Chloroform, Trichloroethylene

B. Non-Volatile or Intravenous anesthetics. They are non-volatile at room temperature and are administered by intravenous route. They are;


Characteristics of G.A

An ideal general anesthetic should possess the following characteristic features:

a) It should be inert

b) It should be potent and non-inflammable
c) It should be non-irritating to mucous membrane

d) It should produce rapid and smooth anesthesia

e) It should produce analgesia and muscle relaxation in addition to anesthesia

f) It should not produce severe hypotension

g) It should not produce nausea and vomiting

h) It should be compatible with adjuvant drugs used in anesthesia

i) It should be economical

j) It should be stable to heat, light and alkalies

Mode of action: General anaesthetics target the ligand gated ion channels and produce the anaesthetic action. The GABA receptor gated chloride channels are the most important sites and opens to perform the inhibitory action. N2O and ketamine do not affect the GABA or glycine gated Cl–channel, but they selectively inhibit the excitatory NMDA-type of glutamate receptor, which belongs to calcium-gated channels in the neurons and leads to neuronal hyperpolarization.

VOLATILE/INHALATION ANAESTHETICS

1. Halothane*
Properties and uses: It is a clear, colourless, heavy, non-flammable liquid, slightly soluble in water, miscible with ethanol, and with trichloroethylene. Halothane lacks flammability. It may produce any depth of anaesthesia without causing hypoxia. Being a non-irritant, its inherent hypotensive effect retards capillary bleeding and renders a comparatively bloodless field. It is a potent, relatively safe general inhalation anaesthetic used in conjunction with N₂O. For skeletal muscle relaxation, it is used with succinyl choline or tubocurarine. It should be stored in well-closed airtight containers, protected from light, at a temperature not exceeding 25°C in a nonreactive metal container.

2. Methoxyflurane

Properties and uses: It is a clear, colourless liquid, nonflammable and nonexplosive in air or oxygen in anaesthetic concentrations. It is the most potent of the inhalational agents. It is employed to cause light anaesthesia with deep analgesic and muscle relaxation feature, which makes it convenient for surgical operations.
3. Enflurane

Properties and uses: It is a clear, colourless, volatile liquid with pleasant hydrocarbon-like odour. Soluble in water, miscible with organic solvents, chemically it is extremely stable. The induction of an emergence from anaesthesia and adjustment of anaesthetic depth during maintenance is smooth and moderately rapid. It is a nonflammable halogenated ether anaesthetic and provides rapid induction with no excitement.

4. Sevoflurane

Properties and uses: Low boiling liquid with a slight odour; miscible with most organic solvents including fats or oils; practically insoluble in water. It is a nonflammable, nonirritating agent. The physical properties of this compound result in a more rapid induction and termination of anaesthetic when observed with the currently used agents.
5. Isoflurane

![Isoflurane Molecular Structure](attachment:image.png)

**Properties and uses:** It is a clear, colourless, heavy liquid, insoluble in water, miscible with ethanol, and trichloroethylene. It resembles isomer enflurane in its properties. It is not flammable in air or oxygen. The depth of anaesthesia can be rapidly adjusted with it. It is used for induction and maintenance of general anaesthesia. Storage: It should be stored in well-closed airtight containers and protected from light.

6. Desflurane

![Desflurane Molecular Structure](attachment:image.png)

**Properties and uses:** Low boiling liquid with a slight odour; miscible with most organic solvents including fats or oils; practically insoluble in water. It is a non-flammable, non-irritating agent. The physical properties of this compound result in a more rapid induction and termination of anaesthetic when observed with the currently used agents.
ULTRA SHORT ACTING BARBITURATES

1. Methohexital sodium*

Methohexital is also a derivative of barbituric acid. It is prepared by condensation of ethylecyanoacetate with 2-chloro-3-pentyne in presence of sodium ethylate yields ethyl-1-methyl-2-pentynyl cyanoacetate which on further condensation with allylbromide yields ethyl(1-methyl-2-pentynyl)allylcynoacetate. Reaction with N-methyl urea yields the iminobarbituric acid which on acid catalyzed hydrolysis forms methohexital.

Synthesis

\[
\text{Diethyl malonate} + \text{3-Bromoprop-1-ene} \xrightarrow{\text{C}_2\text{H}_5\text{ONa}, -\text{HBr}} \text{Methohexital sodium}
\]

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{CH}_3 & \quad \text{C} \quad \text{C} \\
\end{align*}
\]

Prepared by: Mrs. Nisha Dhir
Properties and uses: White to off-white hygroscopic powder, essentially odourless, and the solution is alkaline to litmus, soluble in water. Methohexital produces more rapid recovery from unconsciousness than thiopental. It is more potent and has shorter duration of action. It is used for the induction of anaesthesia through the intravenous administration. It has two advantages over thiopental sodium. First, being it has less affinity towards fatty tissues and second, it has a greater potency. Its onset of action is quite speedy comparable to thiopental sodium while its recovery is more rapid. For these reasons, this intravenous anaesthetic is specifically useful for short surgical operations, such as oral surgery, gynaecological investigation, genitourinary procedures, and electroconvulsive therapy.

2. Thiamylal sodium.

Properties and uses: Thiomylal is a highly hydrophobic thiobarbiturate having its structural features very much related to thiopental. Its biological activities are almost identical to thiopental. It is used as intravenous anaesthetic.

3. Thiopental sodium.
Properties and uses: A yellowish-white powder, hygroscopic, freely soluble in water, and partly soluble in ethanol. These are usually administered intravenously for the production of complete anaesthesia of a short duration. It belongs to the category of ultra short-acting barbiturates. Onset is rapid (about 30 sec) and duration is brief (10–30 min). By rectal route it is administered as a solution, suspension, or suppositories as basal anaesthetic. It is also used as a sedative, hypnotic, and anticonvulsant. It should be stored in well-closed airtight containers and protected from light.

Dosage forms: Thiopental injection B.P.
DISSOCIATIVE ANESTHETICS

Ketamine hydrochloride: Ketamine is a cyclohexanol derivative. Chemically ketamine is (+) 2 (o-chlorophenyl)-2-methylaminocyclohexanone. Ketamine is prepared by Grignard reaction of o-chlorobenzonitrile with bromocyclopentane in presence of strong alkali to form an epoxy compound, which converts to an imine by the action of methylamine. The imine rearranges to ketamine on heating with HCl.

![Chemical Structure of Ketamine Hydrochloride]

Properties and uses: It is a white or almost white crystalline powder, freely soluble in water, methanol, and ethanol. Its another name is ‘dissociative anaesthetic’ because it produces unpleasant hallucinations and strong feelings of dissociation from the environment. It is a rapidly acting nonbarbiturate general anaesthetic that produces anaesthesia and is characterized by profound analgesia.

Storage: It should be stored in well-closed airtight containers, protected from light.

Dosage forms: Ketamine HCl injection I.P., B.P.
NARCOTIC AND NON-NARCOTIC ANALGESICS.

INTRODUCTION: Analgesics are agents that relieve pain by acting centrally to elevate pain threshold without disturbing consciousness or altering other sensory modalities. Certain analgesics like aminopyrine and phenylbutazone also possess anti-inflammatory properties. Such substances and the gold compounds are used in the treatment of arthritis. Many drugs that are used to relieve pain are not analgesics; the general anaesthetics relieves pain by producing unconsciousness, local anaesthetics prevent pain by blocking peripheral nerve fibres, antispasmodics relieve pain by relaxing smooth muscles and the adrenal corticoids relieve pain associated with rheumatoid arthritis by anti-inflammatory action. Analgesics are classified into two major categories:

1. Opioid analgesics or narcotic analgesics (centrally acting).

2. Nonopioid analgesics (peripherally acting).

Opioid Analgesics

Opioid analgesics are drugs that denote all naturally occurring, semisynthetic and synthetic drugs, which have a morphine-like action, namely, relief from pain and depression of CNS associated with the drug dependence. Opium is a dark brown resinous material obtained from the poppy (Papaver somniferum) capsule. It has two types of alkaloids; Phenanthrene derivatives and Benzoisoquinoline derivatives.

Opium has been known from 1500 BC. Sreturner, a pharmacist isolated the active principle of opium in 1806 and named it morphine. Narcotic analgesic agents cause sleep in conjunction with their analgesic effect. If a narcotic is used for a long time, it may become habit-forming (causing mental or...
psychological dependence) and physical dependence may lead to withdrawal side effects. Opioid drugs are not only used as analgesics, but also possess numerous other useful properties. For example, morphine is used to induce sleep in the presence of pain, diarrhoea, suppress cough, and facilitate anaesthesia. The term opioid is used generally to designate collectively the drugs, which bind specifically to any of the subspecies of the receptors of morphine and produce morphine like actions. They tend to produce euphoria, which is an important factor in their addictive property that limits their use. Other limitations include, respiratory depression, decreased gastrointestinal motility leading to constipation, increased biliary tract pressure, and pruritis due to histamine release.

**Mode of action:** The endogenous peptides found in central nervous system (CNS) and gastrointestinal tract (endorphins, enkephalins, dynorphins) can decrease pain (analgesia), produce euphoria, drowsiness, depress respiration, depress the cough reflex, depress gastrointestinal muscle activity. Opiates activate endorphin or enkephalin receptors, which decrease the activity of other neurons that transmit the sensation of pain. At least 5 types of opiate receptors identified. Analgesics are primarily employed for their ability to reduce the perception of pain impulses by the CNS. Analgesic activity is mediated by opiate receptors in the CNS. Five major categories of opioid receptors are known: mu (μ), kappa (κ), sigma (σ), delta (δ), and epsilon (ε). Narcotic drugs occupy the same receptors as endogenous opioid peptides (enkephalins or endorphins). The actions of the narcotic analgesics now available can be defined by their activity at three specific opiate receptor types: mu (μ), kappa (κ) and delta (δ).
μ-(mu) receptors mediate analgesia, euphoria, respiratory and physical depression, miosis, and reduced gastrointestinal motility. These receptors have been further subtyped as μ1, which are supraspinal and mediate analgesia, and μ2 which mediate respiratory depression. The μ1 receptor is morphine selective. δ-(delta) receptors mediate spinal and supraspinal analgesia, dysphoria, psychotomimetic effects (e.g., hallucinations), and respiratory and vasomotor stimulation caused by drugs with antagonist activity. These receptors have been subtyped as δ1 and δ2 and are thought to be relatively unimportant in terms of analgesia.

κ-(kappa) receptors mediate pentazocine like spinal analgesia, sedation, miosis and respiratory depression and dysphoria. These receptors have been further subtyped as κ1 which mediates spinal analgesia, κ3 which mediates supraspinal analgesia and κ2 whose function is unknown. These receptors are proposed to mediate a sedating analgesia with reduced addiction liability and respiratory depression.
Classification: Narcotic analgesics will be classified on the basis of their structural derivation from morphine. They may be classified into following categories:

1. Natural alkaloids of opium: Morphine and codeine.
2. Semisynthetic analogs: Hydromorphone, oxymorphone, oxycodone.
3. Synthetic agents: Meperidine, levorphanol, methadone, sufentanil, alfentanil, fentanyl, remifentanil, levomethadyl.

Morphine and its derivatives.

1. A rigid pentacyclic structure consisting of a benzene ring (A), two partially unsaturated cyclohexane rings (B and C), a piperidine ring (D) and a dihydrofuran ring (E). Rings A, B and C are the phenanthrene ring system. This ring system has little conformational flexibility. Ring A and its 3-hydroxyl group is an important structural feature for analgesic activity. Removal of the 3-OH group reduces analgesic activity by 10-fold.

2. Two hydroxyl functional groups, a C3-phenolic OH (pKa 9.9) and a C6-allylic OH.
3. An ether linkage between C4 and C5.

4. Unsaturation between C7 and C8.

5. A basic, 3°-amine function at position 17.

6. 5 Centers of chirality (C5, C6, C9, C13 and C14) with morphine exhibiting a high degree of stereoselectivity of analgesic action. Only (-)-morphine is active.

**SAR of Morphine was studied by**

1. Modification of alicyclic ring

2. Modification of aromatic ring

3. Modification of 3° Nitrogen

4. Epoxide bridge
1. Modification on alicyclic ring

- The alcoholic hydroxyl group at C-6 when methylated, esterified, oxidized, removed, or replaced by halogen analgesic activity as well as toxicity of the compound increased.

- The reduction of C-6 keto group to C-6 β hydroxyl in oxymorphone gives Nalbupine, it shows antagonistic action of μ receptors.

- The saturation of the double bond at C-7 position gives more potent compound. Examples, Dihydro morphine and Dihydro codeine.

- The 14 β hydroxyl group generally enhances μ agonistic properties and decreases antitussive activity. However, activity varies with the overall substitution on the structure.

- Bridging of C-6 and C-14 through ethylene linkage gives potent derivatives.

- Reaction of thebaine with dienophile (i.e. diel’s alder reaction) results in 6, 14 endoethenotetrahydrothebaine derivatives, which are commonly called ‘oripavines’. Some oripavines are extremely potent μ agonist, for example, Etorphine and Buprenorphine are the best known. These derivatives are about thousand times more potent than morphine as μ agonist.

2. Modification on phenyl ring

- An aromatic phenyl ring is essential for activity.

- Modification on phenolic hydroxyl group decreases the activity.

- Any other substitution on phenyl ring diminishes activity.
3. Modification of 3° nitrogen

- A tertiary amine is usually necessary for good opioid activity.

- The size of the N substitution can dictate the compounds potency and its agonists and its reverse antagonistic property. The N-methyl substitution is having good agonistic property, when increased the size of the substitution by 3–5 carbons results in antagonistic activity. Still larger substituent on N returns agonistic property of opioids, for example, N-phenyl ethyl substitution is ten times more potent than N-methyl groups.

- N-allyl and N-cylo alkyl group leads to narcotic antagonistic property.

4. Epoxide Bridge

- Removal of 3,4 epoxide bridge in morphine structure result in the compound that is referred to as morphinans.

- The morphinans are prepared synthetically. As the synthetic procedure yielded compound is a racemic mixture, only levo isomer possesses opioid activity while the dextro isomer has useful antitussive activity, for example, Levorphanol and Butorphanol.

- Levorphanol is a more potent analgesic than morphine. Summarized SAR of Morphine Analogues is given below:

1. Morphine analogues

   A. Morphine Sulphate
Synthesis

3,4-Dimethoxy-phenylacetic acid

Condensation

Bischler-Napieralski synthesis

POCl₃ - 140°C

Na-Hg/Alcohol

10% HCl

Reflux

Birch reduction

Na⁺(CH₃)₂-C-OH

(i) CH₃

(ii) NaOH

Resolved by (+)-tartaric acid

and (-) form taken

Br₂ - CH₂COOH

7-Bromo codeinone

LiAlH₄/THF

Reflux

Demethylation

C₆H₅N/HCl

Morphine

OH

N

HO

OH

CH₃

N

OH

OH

NH

N

OH

CH₃

N

OH

CH₃

N

OH

N
Properties and uses: It exists as a white or almost white crystalline powder or colourless, silky needles or cubical masses, efflorescent in a dry atmosphere. It is soluble in water, slightly soluble in ethanol, and insoluble in toluene. Morphine is conjugated by hepatic enzyme at phenolic (3-OH) position to from 3-glucuronide metabolite. Glucuronidation of morphine also leads to N-demethylation to normorphine, which has decreased opioid activity and it undergoes N and O conjugation and excreted. Compounds with N-alkyl groups larger than methyl get N-dealkylated as a major route of inactivation. It is used as an opioid receptor agonist and analgesic.

2. Meperidine analogues

Metabolism: Meperidine( Pethidine) analogues results in rapid metabolism. Esterase cleaves the ester bond to leave the inactive 4-carboxylate derivatives. They also undergo N-demethylation to give normeperidine.

SAR of Meperidine Analogues

1. Placement of m-hydroxyl group on the phenyl ring increases activity. The effect is more significant on the keto compound than on the pyridine.

2. Substitution of carbethoxy group in meperidine by acyloxy group provides better analgesic as well as spasmyloytic activity (alpha prodi ne).
3. The presence of phenyl and ester group at 4th position of 1-methylpiperdine results in optimum activity.

4. The replacement of C-4 phenyl group of meperidine by hydrogen, alkyl, other aryl, aralkyl, and hetero cyclic groups reduces analgesic activity.

5. Replacement of phenyl group by phenyl ethyl derivatives is seen to be about three times as active as the meperidine. The amino analogue, anileridine is about four, times more active.

6. Contraction of piperidiene ring to the pyrrolidine gives a more active compound, but causes abuse liability. For example, alphaprodine and procilidine.

7. Enlargement of piperidine ring to a 7-membered hexahydroazepine yield active compounds with low incidence of side effects. For example, Proleptazine.

8. The C-3 methyl analogue with an ester group at the C-4 position like lofentanil 8,400 times more potent than meperidine as an analgesic.

9. In fentanyl, the phenyl and acyl groups are separated by nitrogen. It is 50 times stronger than morphine with minimal side effects. Its short duration of action makes it well suited for use in anaesthesia.

10. The p-chloro analogue (loperamide) has been shown to bind to opiate receptors in the brain, but it cannot penetrate the blood-brain barrier sufficiently to produce analgesia.

11. Diphenoxylate, a structural hybrid of meperidine and methadone type, devoid of analgesic activites. It is effective as an intestinal spasmolytic and is used in the treatment of diarrhoea.
A. Anileridine

Properties and uses: It is a narcotic analgesic, having related chemical structure to that of pethidine. Anileridine is more active than meperidine and has the same uses and limitations. Dose: The usual oral dose is 25 mg every 6 h.

Synthesis

B. Pethidine hydrochloride
Synthesis.

Properties and uses: It is a white crystalline powder, soluble in water, and freely soluble in alcohol. It may be used for the relief of a variety of moderate to severe pain, including the pain of labour and postoperative pain. Pethidine has atropine-like action on smooth muscle. It is normally used to induce both sedation and analgesia simultaneously. It should be stored in well-closed airtight containers and protected from light.

Dose: Usual dose is 50 to 100 mg I.M. Occasionally given orally.

Dosage forms: PethidineHCl injection I.P. PethidineHCl tablets I.P. Pethidine injection B.P., Pethidinetablets B.P.

C. Diphenoxylate hydrochloride
Properties and uses: It is a white or almost white crystalline powder, sparingly soluble in alcohol, very slightly soluble in water, freely soluble in methylene chloride. It is a synthetic analogue of pethidine with some analgesic activity, but is mostly used in the treatment of diarrhoea associated with gastroenteritis, irritable bowel, acute infections, hypermotility, ulcerative colitis, and sometimes even in food poisoning. Storage: It should be stored in well-closed airtight containers and protected from light.

D. Fentanyl Citrate

Synthesis.
Properties and uses: It is a white or almost white powder soluble in water, freely soluble in methanol, and sparingly soluble in alcohol. Fentanyl is related to pethidine and also to basic amilides with analgesic properties, and is characterized by high potency, rapid onset, and short duration of action. It is a potent narcotic analgesic employed for the arrest of pain and it may also be employed as an adjuvant for all such drugs mostly used for regional and general anaesthesia. Storage: It should be stored in well-closed airtight container and protected from light. Dose: By I.M. in preoperative medication 0.05 to 0.1 mg, 30 to 60 min before surgical treatment, for rapid analgesic action, 0.05 to 0.1 mg by IV. Dosage forms: Fentanyl injection B.P.

E. Loperamide.

Properties and uses: It is a white or almost white powder, slightly soluble in water, freely soluble in alcohol and methanol. It is used as a safe and effective opioid derivative with peripherial μ opioid and weak anticholinergic property. Storage: It should be stored in well-closed airtight containers and protected from light.

Dosage forms: Loperamide capsules B.P.


SAR of DiphenylHeptanone (Methadone Series)
• The reduction of keto and acetylation of resulting hydroxyl group gives the acetyl methadol, the useful anti-diarrhoeal opioids, for example, diphenoxylate and loperamide.

• Removal of any of the phenyl group sharply decreases the activity.

• Placement of m-hydroxy group in the phenyl ring decreases analgesic activity.

• The levo-isomer of methadone and isomethadone are twice as effective as their racemic mixture.

• Substitution of terminal dimethylamino group by piperidine group decreases activity.

• Substitution of propionyl group by hydrogen, hydroxyl or acetoxydecreases the activity, whereas amide analogue, pyrrolidinoyl and terminal morpholino moiety enhance the activity by several time.

A. Methadone

![Methadone structure](image)

**Synthesis**
Properties and uses: It is a white or almost white crystalline powder, freely soluble in ethanol and soluble in water. Even methadone, which looks structurally different from other opioid agonists, has steric forces that produce a configuration that closely resembles the opioid agonists. Methadone metabolizes to form an active α-dinormethadol and dinor-L-α-acetylmethadol (LAAM), then it undergoes N-demethylation to form inactive pyrrolidines, an pyrroles which are excreted in urine. Methadone is more active and more toxic than morphine. It can be used for the relief of many types of pain. In addition, it is used as narcotic substitute treatment because it prevents morphine abstinence syndrome. The toxicity of methadone is three to ten times that of morphine, but its analgesic effect is twice that of morphine and ten times that of meperidine.
Storage: It should be stored in well-closed airtight containers and protected from light.

Dosage forms: Methadone HCl injection I.P., Methadone HCl tablets I.P., Methadone injection B.P., Methadone Linctus B.P., Methadone oral solution (1 mg/ml), B.P., Methadone tablets B.P.

B. Propoxyphene hydrochloride

Properties and uses: It is a white or almost white crystalline powder, very soluble in water and freely soluble in alcohol. It has no anti-inflammatory or antipyretic action and has little antitussive activity despite the fact that its levo isomer is used for this purpose. It is used to control mild-to-moderate pain and used along with other analgesics having anti-inflammatory and antipyretic properties, such as paracetamol and aspirin.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dose: The usual does is 65 mg, 3 or 4 times/day.

Dosage forms: Co-proxamol tablets B.P.

SAR of Benzomorphan Derivatives (Benzazocines)

- Pentazocine produces analgesia because of its agonistic action on kappa opioid receptors. Pentazocine is a week antagonistic at μ receptors.

- The trimethyl compound (R1 = R2 = CH3) is more active than dimethyl (R1 = H, R2 = CH3) compound.

- Placement of N-phenyl ethyl results in more activity than N-methyl compound.

- Placement of methyl group in 9th position increases the activity. However, OH group decreases the activity.

- N-allyl (or) N-cycloproyl methyl group confers antagonistic activity. For example, Levallorphanol, Naloxone, and Naltreoxane.

A. Pentazocine
Properties and uses: It is a white or almost white powder sparingly soluble in water, soluble in ethanol, and sparingly soluble in methylene chloride. A synthetic analgesic agent, when administered orally in a 50 mg dose, it appears to be equivalent in analgesic effectiveness to 60 mg of codeine. Pentazocine in a parenteral dose of 30 mg or an oral dose of 50 mg is about as effective as 10 mg of morphine in most patients. There is some evidence that the analgesic action resides principally in the (−) isomer, and a dose of 25 mg is approximately equivalent to 10 mg of morphine sulphate.

B. Levorphanol tartarate.
Narcotic antagonists:

Narcotics are drugs that relieve pain and often induce sleep. The opiates, including opium and drugs derived from opium, such as morphine, codeine, and heroin are narcotics. Narcotics also include certain synthetic chemicals that have a morphine-like action (such as methadone).

Narcotic antagonists are drugs which block the “high” and other effects of narcotics. They also precipitate withdrawal symptoms in the narcotic addict. This feature of narcotic antagonists makes them extremely useful in treating overdoses. They are structurally related to morphine with the exception of the group attached to nitrogen hence they act by competing for the same analgesic receptor sites. Research is currently going on to determine the usefulness of antagonists as maintenance drugs. Present narcotic antagonists (such as naloxone and cyclazocine) have too brief an effect and too many side effects to be completely satisfactory. A new drug, naltrexone, appears to be more promising since its effects last longer, and it appears to be more acceptable to the treatment clients. Narcotic antagonists prevent or abolish excessive respiratory depression caused by the administration of morphine or related compounds. They are also used to treat asphyxia neonatorum and for the diagnosis of possible narcotic addiction.

Naloxone hydrochloride
Properties and uses: It is white or almost white hygroscopic crystalline powder, soluble in water, soluble in ethanol, and insoluble in toluene. It is almost seven times more active than nalorphine in antagonizing the effects of morphine. It shows no withdrawal effects after long-term administration. It lacks not only the analgesic activity shown by other antagonists, but also all of the other agonist effects. At higher doses, Naloxone may be useful in the treatment of shock and spinal cord injury. It should be stored in well-closed airtight containers and protected from light. Usual dose by parenterally 0.4 mg (1 ml)/day. Naloxone injection B.P., Neonatal naloxone injection B.P.

Nalorphine hydrochloride

Synthesis
Properties and uses. Nalorphine is available as hydrochloride salt. Nalorphine hydrochloride is white colored, odorless, crystalline powder. It darkens on exposure to light. It is soluble in water, dilute alkali hydroxide solution but insoluble in chloroform and ether. It must be kept in tightly closed light resistant containers. Nalorphine is a narcotic antagonist used to treat narcotic-induced respiratory depression. It is administered by intravenous injection for treating the overdosage of morphine, pethidine, methadone and levorphanol. Nalorphine precipitates withdrawal symptoms and produces behavioral disturbances in addition to the antagonism action.

Levallorphan tartarate. Levallorphan is available as tartarate salt. Levallorphan tartarate occurs as white colored, odorless, crystalline powder. It melts at 175°C and is slightly soluble in water but insoluble in ether and chloroform.
**ANTI-INFLAMMATORY AGENTS**

*(Non-Steroidal Anti-inflammatory Drugs) (NSAIDs)*

**Introduction:** The non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of minor pain and for the management of edema and tissue damage resulting from inflammatory joint disease (arthritis). A number of these drugs possess antipyretic activity in addition to having analgesic and anti-inflammatory actions, and thus have utility in the treatment of fever. Some of the primary indications for NSAID therapy include: Rheumatoid arthritis, osteoarthritis (OA), acute gouty arthritis, ankylosing spondylitis, dysmenorrhea and tissue damage resulting from inflammatory joint disease (arthritis).

**Role of COX enzymes in inflammation**

Two COX isoenzymes have been identified: COX-1 and COX-2.

COX-1 constitutive enzyme is present in a wide variety of cell types and influences the “housekeeping” functions of prostaglandins. This activity is particularly important in the gastrointestinal (GI) tract, the kidneys, and the circulatory system.

COX-2, on the other hand, is inducible enzyme, is found in only a few cell types, especially macrophages and other leukocytes, fibroblasts, and endothelial cells, including those of the vascular system. COX-2 is involved in those aspects of the inflammatory process that are mediated by prostaglandins.
1. The major mechanism by which the NSAIDs elicit their therapeutic effects (antipyretic, analgesic, and antiinflammatory activities) is inhibition of prostaglandin (PG) synthesis. Specifically NSAIDs competitively (for the most part) inhibit cyclooxygenases (Prostaglandin synthetase), the enzymes that catalyze the synthesis of cyclic endoperoxides from arachidonic acid to form prostaglandins.

2. Generally, the NSAIDs inhibit both COX-1 and COX-2. Most NSAIDs are mainly COX-1 selective (e.g., aspirin, ketoprofen, indomethacin, piroxicam, sulindac). Others are considered slightly selective for COX-1 (e.g., ibuprofen, naproxen, diclofenac) and others may be considered slightly selective for COX-2 (e.g., etodolac, nabumetone, and meloxicam). The mechanism of action of celecoxib and rofecoxib is primarily selective inhibition of COX-2; at therapeutic concentrations, the COX-1 isoenzyme is not inhibited thus GI toxicity may be decreased.
3. Other mechanisms that may contribute to NSAID anti-inflammatory activity include the reduction of superoxide radicals, induction of apoptosis, inhibition of adhesion molecule expression, decrease of nitric oxide synthase, decrease of pro-inflammatory cytokine levels (tumor necrosis factor-α, interleukin-1), modification of lymphocyte activity, and alteration of cellular membrane functions.

Classification of NSAID’S


4. Anthranilic acid derivatives: Mefenemic acid, Flufenemic acid, Meclofenamate.

5. Aryl alkanoic acid derivative.
   a. Indole acetic acid: Indomethacin.
   b. Indene acetic acid: Sulindac.
   c. Pyrrole acetic acid: Tolmetin, Zormipirac.
   d. Phenyl acetic (propionic) acid: Ibuprofen, Diclofenac, Naproxen, Caprofen, Fenoprofen, Keto-profen, Flurbiprofen, Ketorolac, Etodaolac.

7. **Selective COX-2 inhibitors:** Celecoxib, Rofecoxib, Valdecoxib.

8. **Gold compounds:** Auronofin, Aurothioglucose, Aurothioglucamide, Aurothiomalate sodium.

9. **Miscellaneous:** Nabumetone, Nimesulide, Analgin.

10. **Drug used in gout:** Allopurinol, Probenecid, sulphipyrazone.

1. **Salicylates:**

**Structure and chemistry:** The salicylates are derivatives of 2-hydroxybenzoic acid (salicylic acid). They were discovered in 1838 following the extraction of salicylic acid from willow bark. Salicylic acid was used medicinally as the sodium salt but replaced therapeutically in the late 1800s by acetylsalicylic acid (aspirin).

**Structural Activity Relationship (SAR) of Salicylates**

1. The active moiety of salicylates is salicylate anion, side effects of aspirin, particularly GIT effects appear to be associated with the carboxylic acid functional group.

2. Reducing the acidity of the carboxy group results in a change in the potency of activity. Example—the corresponding amide (salicylamide) retain the analgesic action of salicylic acid, but is devoid of anti-inflammatory properties.

3. Substitution on either the carboxyl or phenolic hydroxyl group may affect the potency and toxicity. Benzoic acid itself has only week activity.
4. Placement of the phenolic hydroxyl group at meta or para to the carboxyl group abolish the activity

**Mechanism of Action.** The salicylates have potent anti-inflammatory activity with mild analgesic and antipyretic activities. These compounds are mainly COX-1 selective—they are bound with higher affinity to COX-1. The therapeutic and some of the toxic actions (i.e. gut) of aspirin can be related to its ability to inhibit COX-1 in various tissues and participate in transacetylation reactions in vitro

**a. Sodium salicylate.**

![Sodium Salicylate Structure](image)

**Properties and uses:** Sodium salicylate is a white crystalline powder, soluble in water, sparingly soluble in alcohol. It is used for fever and for the relief of pain. It also possesses anti-inflammatory actions similar to aspirin and symptomatic therapy of gout.

**b. Aspirin.** Acetylsalicylic acid is an acetyl derivative of salicylic acid. It was introduced into medicine by Dreser in 1899. Acetyl salicylic acid (aspirin) can be prepared by the reaction between salicylic acid and acetic anhydride. In this reaction, the hydroxyl group on the benzene ring in salicylic acid reacts with acetic anhydride to form an ester functional group. Thus, the formation of acetyl
salicylic acid is referred to as an esterification reaction. This reaction requires the presence of an acid catalyst.

Properties and uses: Aspirin is a white crystalline powder, slightly soluble in water and soluble in alcohol, indicated for the relief of minor aches and mild-to-moderate pain in the conditions such as arthritis and related arthritic condition. Also used in myocardial infarction prophylaxis. Usual adult dose: 300 to 650 mg every 3 or 4 h orally or 650 mg to 1.3 g as the sustained-release tablet every 8 h; rectal, 200 mg to 1.3 g three or four times a day. Dosage forms: Aspirin tablets I.P., B.P., Dispersible aspirin tablets B.P., Effervescent soluble aspirin tablets B.P., Gastro-resistant aspirin tablets B.P., Aspirin and Caffeine tablets B.P., Co-codaprin tablets B.P., Dispersible co-codaprin tablets B.P.

2. Anthranilic acid derivatives: Anthranilates are considered to be N-aryl substituted derivatives of anthranilic acid, which is a bioisostere of salicylic acid. These agents retain the acidic properties that are characteristic of this class of agents. The most active fenamates have small alkyl or halogen substituents at the 2′, 3′ and/or 6′ position of the N-aryl moiety (meclafenamate is 25 times more potent than mefenamate). Among the disubstituted N-aryl fenamates the 2′, 3′-derivatives are most active suggesting that the substituents at the 2′, 3′-positions serve to force the N-aryl ring out of coplanarity with the anthranilic acid. Hence this steric effect is proposed to be important in the effective interaction of the fenamates at their inhibitory site on cyclooxygenase.
SAR of Anthranilic Acid Derivatives (Fenamates)

1. The position of the carboxyl function is important for the activity of anthranilic acid derivatives that are active, whereas the 3 and 4 amino benzoic acid analogues are not active.

2. Replacement of carboxylic acid function with the tetrazole results in the retention of antiinflammatory activity.

3. Placement of substitution on the anthranilic acid ring generally reduces the activity.

4. Substitution on the N-aryl ring can lead to conflicting results. In the ultraviolet erythema assay for anti-inflammatory activity, the order of activity was generally 3´ > 2´ > 4´ for mono substitution with CF₃ group (flufenamic acid) being particularly potent.

5. In disubstituted derivatives, where the nature of the two substitutes is the same 2´, 3´-disubstitution appears to be the most effective (mefenemetic acid).
6. The NH moiety of anthranilic acid is essential for the activity as the replacement of NH function with O, CH₂, S, SO₂, N-CH₃, or NCOCH₃ functionalities significantly reduced the activity.

**MODE OF ACTIONS.** The anthranilates have primarily antiinflammatory with some analgesic and antipyretic activity and are non-COX selective. The anthranilates are used as mild analgesics and occasionally to treat inflammatory disorders. Diclofenac is used for rheumatoid arthritis, osteoarthritis and post-operative pain and mefenamic acid as an analgesic for dysmenorrhea. The utility of this class of agents is limited by a number of adverse reactions including nausea vomiting, diarrhoea, ulceration, headache, drowsiness and hematopoietic toxicity.

a. Mefenamic acid*

![Mefenamic acid](image)

**Synthesis of mefenamic acid.** Mefenamic acid can be prepared by following reactions:

1. **COOH**
2. **Cl**
3. **H₂N**
4. **CH₃**
5. **CH₃**

![Reaction](image)
Properties and uses: Its metabolism occurs through regioselective oxidation of 3-methyl group and glucuronidation of mefenamic acid. Majority of the 3-hydroxy methyl metabolite and dicarboxylic acid products are excreted. It is used as an analgesic and anti-inflammatory agent.

b. Meclofenamate.

\[
\text{COONa} \quad \begin{array}{c}
\text{N} \\
\text{Cl} \\
\text{CH}_3
\end{array} 
\]

Properties and uses: Its metabolism occurs through regioselective oxidation of 3-methyl group and glucuronidation of mephanamic acid. Majority of the 3-hydroxy methyl metabolite and dicarboxylic acid products are excreted. It is used as an analgesic and anti-inflammatory agent.

3. Arylalkanoic Acids

SAR of Arylalkanoic Acids

\[
\begin{array}{c}
\text{Ar} \\
\text{H} \\
\text{H}
\end{array} 
\]
1. The centre of acidity is usually located one carbon atom adjacent to a flat surface represented by an aromatic or hetero aromatic ring.

2. The distance between these centres is critical because increasing this distance to two or three carbons generally decreases activity.

3. All agents possess a centre of acidity, which can be represented by a carboxylic acid and hydroxamic acid, a sulphonamide or a terazole.

4. Substitution of a methyl group on the carbon atom separating the aromatic ring leads to enhancement of anti-inflammatory activity.

A. Indole acetic acid derivatives

a. Indomethacin.

SAR of Indole Acetic Acid Derivatives.
1. Placement of other acidic functionalities instead of the carboxyl group decreases activity and the amide derivatives are inactive.

2. Substituents of R1 useful for increasing anti-inflammatory activity are ranked as \( \text{C}_6\text{H}_4\text{CH}_2 > \text{alkyl} > \text{H} \).

3. Acylation of the indole nitrogen with aryl/alkyl carboxylic acids results in the decrease of activity.

4. Presence of substituents on the N-benzoyl derivatives in the p-position with F, Cl, CF₃, or S-CH₃ groups provide greatest activity.

5. X substituents activity are ranked as 5-OCH₃ > N(\text{CH}_3)_2 > \text{CH}_3 > \text{H}.

6. The presence of indole ring nitrogen is not essential for activity because the corresponding 1-benzylidenylindene analogue (sulindac) is also active.

7. Alkyl groups especially methyl group at 2nd position is much active than aryl substituted analogues.

8. Substitution of a methyl group at the \( \alpha \) position of the acetic acid side chain leads to equiactive analogues.

9. Anti-inflammatory activity was displayed only by the dextrorotatory enantiomer with similar absolute configuration; it has 25 times the activity of phenylbutazone.

**Properties and uses:** It is a white or yellow crystalline powder, insoluble in water and sparingly soluble in alcohol. Indomethacin is more effective than aspirin. The most frequent side effects are gastric distress and headache. It also has been associated with peptic ulceration, blood disorders, and possible death...
(these side effects appear to be closely related and sometimes can be minimized by reducing the dose). It is not recommended for use in children because of possible interference with the resistance to infection. Used as anti-inflammatory and analgesic in rheumatic arthritis, spondylitis, and to lesser extent in gout. Relieved. As an antirheumatic by oral route, the dose is 50 mg two or three times a day. And as an antipyretic, the dose is orally 25–50 mg three times a day. Indometacin capsules I.P., B.P., Indometacin Suppositories I.P., B.P.

B. Indeneacetic acid derivatives

a. Sulindac.

Properties and uses: Sulindac is a yellow crystalline powder, very slightly soluble in water, soluble in methylene chloride, and dilute solutions of alkali hydroxides, sparingly soluble in alcohol. The (Z) isomer of sulindac showed much more potent anti-inflammatory activity than the corresponding (E)-isomer. The more polar and inactive sulphoxide is virtually the only form excreted. It is a prodrug to form active metabolites of sulphite. In addition to it, sulindac is oxidized to corresponding sulphone and other sulphone-glucuronide conjugates. It has analgesic, antipyretic, and anti-inflammatory properties. It is usually employed in the treatment of rheumatic and muscular skeletal disorders, acute gouty arthritis, and osteoarthritis.
C. Pyrrole acetic acid derivative: Replacement of the p-tolyl group with a p-chloro benzoyl moiety produced little effect on activity, whereas introduction of a methyl group in the 4th position and 5-p-chloro benzoyl analogues (zomeapirac) proved to be four times potent as tolmetin.

a. Tolmetin

Properties and uses: It is a light yellow, crystalline powder, soluble in water, slightly soluble in alcohol. It has antipyretic, analgesic, and anti-inflammatory actions. It is employed in the treatment of rheumatic and musculoskeletal disorders. The drug is, however, comparable to indomethacin and aspirin in the control and management of disease activity. Adult oral dose initially is 400 mg three times a day, subsequently adjusted as per patient’s response.

b. Zomepriac

Properties and uses: A greater degree of analgesia for severe pain is claimed for Zomepirac. It is used as an analgesic and an ant-inflammatory drug. It is four times as potent as tolmetin. Dose is 400 to 600 mg of zomepirac daily (zomepirac sodium 1.2 g is approximately equivalent to 1 g of zomepirac).
D. Aryl and heteroaryl acetic/propionic acid derivatives.

a. Diclofenac.

Properties and uses: Diclofenac sodium is a white or slightly yellowish crystalline slightly hygroscopic powder, sparingly soluble in water, soluble in methanol and alcohol, slightly soluble in acetone. Used in the treatment of rheumatic arthritis. The usual dose is 20–50 mg three times a day. It can also be given as a suppository.

b. Ketorolac.

Properties and uses: Ketorolac is a white crystalline powder, soluble in water and in methanol, slightly soluble in ethanol, practically insoluble in methylene chloride. Ketorolac is a potent analgesic indicated for the treatment of moderately severe and acute pain. The dose for ocular itching, which is associated with seasonal allergic conjunctivitis, for reduction of ocular pain, and for photophobia in patients undergoing incisional refractive surgery, instil one drop of a 0.5% solution into the affected eyes four times daily.
**Ibuprofen**

![Ibuprofen structure](image)

**Synthesis**

\[
\text{Isobutyl benzene} \xrightarrow{(\text{CH}_3\text{CO})_2\text{O}} \text{P-Isobutyl acetophenone} \xrightarrow{\text{HCN}} \text{Ibuprofen} \]

**Properties and uses:** Ibuprofen is a white crystalline powder or colourless crystals, practically insoluble in water, soluble in acetone, methanol, methylene chloride, and dilute solutions of alkali hydroxides and carbonates. The precursor Ibufenac, which was abandoned owing to hepatotoxicity, was less potent. Furthermore, these isomers are the more potent inhibitors of PG synthetase. It is an anti-inflammatory drug that possesses antipyretic and analgesic action and is used for the treatment of rheumatoid arthritis and osteoarthritis. Usual oral adult dose as an analgesic (dysmenorrhoea) is 200–400 mg four to six times a day; in rheumatoid arthritis and osteoarthritis. The dose is 300–400 mg three or four times a day. Ibuprofen tablets I.P., B.P, Ibuprofen cream B.P., Ibuprofen gel B.P., Ibuprofen oral suspension B.P.
d. Naproxen

\[
\text{\textbf{Properties and uses:}} \text{ Naproxen is a white crystalline powder, practically insoluble in water, soluble in ethanol and in methanol. The drug is fairly comparable to aspirin both in the management and control of disease symptoms. Nevertheless, it has relatively lesser frequency and severity of nervous system together with milder GI-effects. It possesses analgesic, anti-inflammatory, and antipyretic actions, and it is used in the treatment of rheumatic arthritis, dysmenorrhea, and acute gout. Dose: For adult in rheumatoid arthritis, 250–375 mg as initial dose two times a day; in acute gout, 750 mg as loading dose followed by 250 mg three times a day until relieved. Dosage forms: Naproxen oral suspension B.P., Naproxen suppositories B.P., Naproxen tablets B.P., Gastro resistant naproxen tablets B.P.}
\]

4. Oxicams: The term oxicam described the relatively new enolic acid class of 4-hydroxyl -1,2benzothiazinecarboxamidewith anti-inflammatory and analgesic properties.
Piroxicam.

Properties and uses: Piroxicam is a white or slightly yellow crystalline powder, practically insoluble in water, soluble in methylene chloride, and slightly soluble in ethanol. It is employed for acute and long-term therapy for the relief of symptoms of osteoarthritis and rheumatoid arthritis. It also possesses uricosuric action and has been used in the treatment of acute gout.

5. SAR of p-amino Phenol Derivatives

1. Etherification of the phenolic function with methyl or propyl groups produces derivatives with greater side effects than ethyl derivatives.

2. Substituents of the nitrogen atom, which reduce the basicity, also reduce activity unless the substituent is metabolically labile. Example—acetyl groups.

3. Amides derived from aromatic acid. Example—N-phenyl benzamides that are less active or inactive.

Phenacetin
Properties and uses: It exists as a white glistering powder with a bitter taste, sparingly soluble in water and soluble in chloroform. It is an analgesic and an antipyretic with similar effectiveness as an aspirin. It has a greater potential for toxicity (hemolytic anaemia and methemoglobinaemia) than paracetamol. Usual dose as oral for adults is 300 mg to 2 g per day.

Acetaminophen.

\[
\text{Para-nitro phenol} \xrightarrow{\text{Reduction}} \text{Para-aminophenol} \xrightarrow{\text{Glacial acetic acid}} \text{Paracetamol}
\]

Properties and uses: Paracetamols exist as white crystalline powder, sparingly soluble in water, soluble in alcohol, and very slightly soluble in methylene chloride. Paracetamols produce antipyresis by acting on the hypothalamic heat-regulating centre and analgesia by elevating the pain threshold. Hepatic necrosis and death have been observed following over dosage; hepatic damage is likely in an adult who takes more than 10 g in a single dose or if a 2-year old child takes more than 3 g.: Usual oral adult dose is 500 mg to 1 g for three or four times a day. Paracetamol tablets I.P, B.P., Paracetamol syrup I.P., Co-codamol tablets B.P., Effervescent Co-codamol tablets B.P., Co-dydramol tablets B.P.,
Co-proxamol tablets B.P., Paracetamol capsules B.P., Paediatric paracetamol oral solution B.P., Paracetamol oral suspension B.P., Paracetamol suppositories B.P., Dispersible paracetamol tablets B.P., soluble paracetamol tablets B.P.

**Antipyrine.** Antipyrine is 2, 3-dimethyl-1-phenyl-3-pyrazolin-5-one. It was one of the first synthetic compounds to be used in medicine.

![Chemical structure of Antipyrine](image)

**Properties and uses:** Antipyrine is available as colorless, crystalline powder or white powder. It is odourless and having slightly bitter taste. It is freely soluble in water, alcohol, and chloroform. Antipyrine has analgesic, anti-inflammatory and antipyretic activities.

6. 3, 5-Pyrazolidinediones.

**SAR of 3, 5-Pyrazolidinediones.**

1. Replacement of one of the nitrogen atom in the pyrazolidinediones with an oxygen atom yields isoxazole analogues, which are as active as pyrazolidinediones derivatives.

2. In 3, 5-pyrazolidinedione derivatives, pharmacological activities are closely related to their acidity, the dicarbonyl function at the 3rd and 5th positions enhance the acidity of hydrogen atom at the 4th position.
3. Presence of a keto group in the γ-position of the butyl side chain produces the active compound.

4. Decreasing or eliminating acidity by removing the acidic proton at 4th position (e.g. 4, 4-dialkyl derivatives) abolishes anti-inflammatory activity. Thus, if the hydrogen atom at the 4th position of phenyl butazone is replaced by substituents, such as a methyl group, antiinflammation activity is abolished.

5. If acidity is enhanced too much, anti-inflammatory and sodium-retaining activities decrease while other properties, such as the uricosuric effect increases.

6. Introduction of polar function in these alkyl groups give mixed results. The γ-hydroxy-n-butyl derivative possesses pronounced uricosuric activity, but give fewer anti-inflammatory effects.

7. Substitution of 2-phenyl thio ethyl group at the 4th position produces antigout activity (sulphinpyrazone).

8. Presence of both the phenyl groups is essential for neither anti-inflammatory nor analgesic activity.

9. m-Substitution of aryl rings of the phenyl butazone gives uniformly inactive compounds. p-Substitution, such as methyl, chloro, nitro, or OH of one or both rings retains activity

a. Phenylbutazone
Properties and uses: Phenylbutazone is a white crystalline powder, practically insoluble in water, sparingly soluble in alcohol, and soluble in alkaline solutions. It is a pyrazole derivative that has antipyretic, analgesic, and anti-inflammatory actions, because of its toxicity it is not used as a general antipyretic or analgesic. It is a usual practice reserved for use in the treatment of osteoarthritis, ankylosing spondylitis, arthritis, acute superficial thrombophlebitis, painful shoulder, and Reiter’s disease, where less toxic drugs have failed. The usual dose is 100–600 mg per day.