Lecture Notes on

Drugs acting on Central Nervous System

(Unit III)

[As per VCI MSVE 2016 Syllabus]

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Unit III

DRUGS ACTING ON CENTRAL NERVOUS SYSTEM

Syllabus

Chapter 1 : Classification of drugs acting on CNS.

Chapter 2 : History, mechanism and stages of general anaesthesia. Inhalant, intravenous and dissociative anaesthetics.

Chapter 3 : Hypnotics and sedatives.

Chapter 4 : Psychotropic drugs, anticonvulsants,

Chapter 5 : Analgesics - opioid analgesics, non-steroidal anti-inflammatory drugs.

Chapter 6 : Analeptics and other CNS stimulants.

Chapter 7 : Drugs acting on somatic nervous system: Local anaesthetics, muscle relaxants. Euthanizing agents.

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Suggested Text books of Pharmacology:

1. Veterinary Pharmacology & Therapeutics (10th Edn.-2018) – Jim E. Riviere and Mark G. Papich
2. Essentials of Medical Pharmacology (8th Edn.-2019) – K.D. Tripathi
3. Rang & Dale's Pharmacology (9th Edn.- 2019) – James M. Ritter, Rod Flower, Graeme Henderson, Yoon Kong Loke, David MacEwan & Humphrey P. Rang.
4. Goodman & Gilman's The Pharmacological Basis of Therapeutics (13th Edn.-2018) – Laurence L. Brunton, Randa Hilal-Dandan & Björn C. Knollmann.

Chapter - 1

Introduction to Drugs acting on C.N.S

DRUGS ACTING ON C.N.S.

CLASSIFICATION OF DRUGS ACTING ON CENTRAL NERVOUS SYSTEM:

Primary Classification	Sub-classification	Examples
C.N.S. STIMULANTS	Spinal Stimulants	Strychnine, Brucine, Picrotoxin
	Medullary Stimulants (Analeptics)	Doxaprm, Bemegride, Picrotoxin, Nikethamide, Leptazol
	Cortical Stimulants:	
	Classical cortical stimulants	Cocaine, Dexamphetamine, Xanthines
	Psychotomimetics	Mescaline, LSD
	Antidepressants (Thymoleptics)	Imipramine, Desipramine, Phenelzine, Iproniazid, Tranylcypramine
C.N.S. DEPRESSANTS	Tranquillizer sedatives (Neuroleptics, Ataractics, Tranquillizers)	Phenothiazines (Promazine, Acepromazine, Chlorpromazine, Promethazine) Butyrophenones (Azaperone, Droperidol, Haloperidol, Haloanisone) Rauwolfia alkaloids (Reserpine)
	Hypnotic sedatives (Classical sedatives)	Chloralhydrate, Xylazine, Detomidine, Medetomidine, Phenobarbitone, Diazepam, Zolazepam.
	General Anaesthetics:	
	Gases	Nitrous oxide, Cyclopropane, Ethylene
	Volatile liquids	Ether, Halothane, Enflurane, Isoflurane, Chloroform, Methoxyflurane etc.
	Solids (Injectables)	Barbiturates (Pentobarbitone, Thiopentone, Thiamylal, Methohexitone etc.) Saffan, Propanidid, Minoxolone.
	Dissociative Anaesthetics	Phencyclidine, Ketamine, Tiletamine.
	Anxiolytics	Benzodiazepines (Diazepam, Clonazepam)
	Central muscle relaxants	Guaiphenesin, Mephenesin.
	Anticonvulsants (Antiepileptics)	Phenobarbitone, Phenytoin, Diazepam, Carbamazepine, Ethosuximide, Acetazolamide etc.
	Analgesics	
	Analgesic-antipyretic-antiinflammatory agents	Acetylsalicylate, Salicylate, Phenylbutazone, Isopyrin, Ibuprofen, Naproxen, Flunixin, Piroxicam, Meloxicam, Flufenamate etc.
	Narcotic analgesics (Sedative analgesics)	Morphine, Codeine, Heroin, Pethidine, Methadone, Fentanyl, Etorphine, Butorphanol, Buprenorphine, Pentazocine etc.
	[Morphine (analgesic) antagonists – Nalorphone, Diprenorphine, Naloxone, Naltrexone etc.]	
	Neuroleptanalgesics	Etorphine+Acepromazine Etorphine+Methotrimeprazine Fentanyl+Haloanisone Fentanyl+Droperidol

DEFINITIONS:

Analeptics (medullary stimulants):

Drugs that stimulate a depressed respiratory centre to produce increased respiratory exchange. These are employed in the treatment of barbiturate poisoning, drowning, neonatal asphyxia, heat or lightening stroke and threatened respiratory collapse during anaesthesia.

Psychotomimetics:

These are agents that produce effects which resemble certain psychotic states. They differ from classical cortical stimulants in that there are no signs of marked hyperexcitability. Hallucinations and delusions occur in response to these drugs.

Thymoleptics (Antidepressants or Mood elevators):

These produce mild stimulation of higher centres but do not cause symptoms of marked hyperexcitability even at high dose levels. They are thus rather aptly called antidepressants rather than stimulants – they elevate mood. Thymoleptics are used in man to treat psychotic depressions.

Anxiolytics:

These abolish or relieve feeling of anxiety in human subjects. In man, they are used to treat neuroses.

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C. N. S. TRANSMITTERS

The function of the neurons in the CNS is regulated by the chemicals called neurotransmitters. These chemicals are also called as neuroregulators or neuromodulators. The neuromodulators may be defined as chemicals which regulate pre-synaptic transmitter release and also control post-synaptic neuronal excitability.

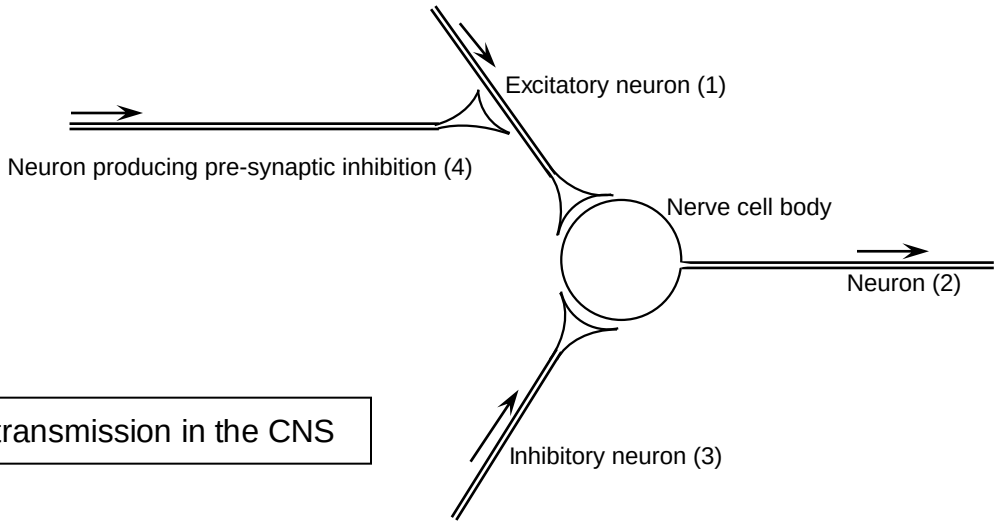

Fig.: Showing transmission in the CNS

Transmission in the CNS occurs in the following general ways:

1. Release of excitatory transmitter by neuron (1) causing depolarization of the post-synaptic membrane of neuron (2) and conduction of nerve impulse by neuron (2) [Post-synaptic excitation];
2. Release of inhibitory transmitter by neuron (3), causing hyperpolarization of post-synaptic membrane of neuron (2) and block of conduction of nerve impulse by neuron (2) [Post-synaptic inhibition]; or
3. Release of inhibitory transmitter by neuron (4) causing partial, small, long-lasting depolarization of nerve endings of an excitatory neuron (1). This in turn reduces the quantity of excitatory transmitter released on the post-synaptic membrane of neuron (2) [Pre-synaptic inhibition].

CLASSIFICATION OF CNS TRANSMITTERS:

Over 40 different neurotransmitter substances have been identified. They are usually classified into two major groups:

1. **Small-molecule, rapidly acting neurotransmitters:** The small-molecule, rapidly acting transmitters are the ones of most concern to us. They are synthesized in the cytosol of the presynaptic terminal and cause most of the responses in the CNS. Their actions on receptors usually occur within a millisecond or less after release. Afterward they either are destroyed (degraded) locally by enzymes, diffuse out of the cleft, or are absorbed by active transport back into transmitter vesicles (i.e. reuptake).

Summary of small-molecule neurotransmitters located in the CNS:

Transmitter	Anatomic location in CNS	Receptor subtypes	Predominant postsynaptic action
Acetylcholine	Cell bodies at all levels	Yes	Excitatory (and inhibitory)
Monoamines			
Norepinephrine	Cell bodies in pons & brain stem	Yes	Excitatory (and inhibitory)
Dopamine	Cell bodies at all levels	Yes	Inhibitory
5-hydroxytryptamine (Serotonin)	Cell bodies in brain stem & pons	Yes	Inhibitory (and excitatory)
Amino acids			
γ-aminobutyric acid (GABA)	Supraspinal interneurons involved in presynaptic inhibition	Yes	Inhibitory
Glycine	Spinal & brain stem interneurons	--	Inhibitory
Glutamate & aspartate	Relay neurons at all levels	--	Excitatory

2. **Slowly acting neuropeptide neurotransmitters:** The larger group of neurotransmitters comprises the neuropeptides, which are very potent, slower to act, and present in much smaller quantities than the small-molecule transmitters. They are synthesized by ribosomes in the neuronal cell body.
   Examples of neuropeptide neurotransmitters located in the CNS are – β–Endorphins, Vasopressin, Oxytocin, Growth hormone, Enkephalin, Somatostatin, Substance P, Cholecystokinin, Angiotensin II and Neurotensin.

ACETYLCHOLINE (ACh):

Acetylcholine is widely distributed throughout the CNS. The mechanisms by which acetylcholine functions as a synaptic transmitter in the CNS are similar to those operant in the periphery (e.g., the neuromuscular junction). The transmitter is released from the vesicles at the presynaptic terminal and diffuses across the synaptic cleft to act upon post-synaptic receptors. It is then inactivated via hydrolysis (acetylcholinesterase). As in the periphery, cholinergic receptors are of two classes: muscarinic and nicotinic. To date five muscarinic receptors (M_1 – M_5) are known, and M_1 is abundant in the brain. Recently, nicotinic cholinergic receptors have also been identified in the CNS.

Enhanced cholinergic activity (in association with excess dopamine activity) causes Parkinson's disease and loss of cholinergic neurons in CNS results in dementia (Alzheimer's disease type) in man.

NOREPINEPHRINE (NE):

Unlike ACh, NE has an uneven distribution in the CNS. Two regions of the CNS that are most important in this regard are the locus cerulus (caudal central gray matter of the brain stem) and the lateral and ventral trigeminal regions of the medulla (reticular formation). From neurons arising in these locations, axons innervate target cells in cortical, subcortical and spino-medullary fields.

NE is considered important in control of sleep and wakefulness, mood and emotional behavior, and temperature, among other functions. In most but not all of these areas NE probably activates excitatory receptors.

Functional deficiency of NE in CNS results in depression and its excess causes mania and arousal reactions (wakefulness and alertness). Reserpine depletes NE stores causing CNS depression.

DOPAMINE:

In the CNS dopamine is a major neurotransmitter in addition to its role as a precursor in the synthesis of NE. It is distributed heterogeneously throughout the CNS. The largest concentration of dopamine in the brain is in the basal ganglia and the limbic system. Dopamine in the CNS is linked to fine control of movement, to disturbances of behavior, and to the hypothalamic-pituitary endocrine system. Dopamine has primarily an inhibitory function.

Dopaminergic neurons control both motor and behavioural changes. Its deficiency results in Parkinson's disease and its excess causes Schizophrenia and Huntington's chorea in man. Dopamine inhibits release of prolactin and increased secretion of growth hormone from anterior pituitary.

5-HYDROXYTRYPTAMINE (5-HT):

It causes hallucinatory behaviour, antidepressant effect and inhibition of pain sensation. Hypothalamus is rich in 5-HT, where it regulates body temperature. Its secretion raises body temperature and inhibits production of hypothalamic factors such as gonadotropin release and growth hormone release inhibitory factors.

HISTAMINE:

Its actions are through stimulation of H_1 and H_2 receptors which mediate excitatory and inhibitory actions, respectively.

AMINO ACIDS:

Certain amino acids function as neurotransmitters in brain and spinal cord. Glutamate and aspartate mediate excitatory transmission in synapses. Glutamate is widely distributed. These amino acids may have a role in the genesis of epilepsy.

The inhibitory amino acids are GABA and glycine. GABA is the main inhibitory transmitter in brain. Its actions are through post-synaptic $GABA_B$ and pre-synaptic $GABA_A$ receptors. Picrotoxin produces convulsions through blockage of $GABA_A$ receptors, and diazepam produces depression through facilitation of GABA transmission. Glycine is the inhibitory transmitter in spinal cord. Strychnine produces convulsions by acting as glycine antagonist and tetanus toxin acts by interfering with glycine release.

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Chapter - 2

Anaesthesia and Anaesthetics

A N A E S T H E S I A

Anaesthesia = Aneis + thesia (Greek words) = Loss of feeling or no feeling.
Def. of Anaesthesia: It is an art and science of producing insensibility to the patient.

General Anaesthesia: General anaesthesia is a state of unconsciousness produced by a process of controlled, reversible, drug-induced intoxication of the central nervous system in which the patient neither perceives nor recalls noxious stimuli.

Euthanasia: (Irreversible) It is the humane killing or mercy killing of animals suffering from incurable diseases.

Purpose of Anaesthesia:

The purpose of anaesthesia is to provide a safe, convenient and inexpensive means of restraint to enable clinical procedures to be performed with the minimum of pain, discomfort and toxicity to the patient and the anaesthetist.

HISTORY OF ANAESTHESIA:

The practice of anaesthesia is followed since the ancient times. Drugs of various kinds have been used for many centuries to reduce the distress of surgical operations. Arabian physicians used drugs like opium and henbane. Alcohol was also used to dull sensation – during emergency amputations performed in wartime, strong rum was often administered to the patients.

- ✓ The 1st anaesthetic nitrous oxide (laughing gas) was discovered by Priestley in the year 1776. Humphrey Davy declared the ability of N_2O in removing pain and suggested for its use in painless surgery in 1799.
- ✓ Crawford Long, a US physician, operated on a tumour on the neck of a friend under ether anaesthesia in 1842. A ledger entry was made to establish his priority as the first man to use an anaesthetic for a surgical operation, though the credit for this is often given to the person who demonstrated it in public.
- ✓ Horace wells demonstrated that N_2O could be used as an anaesthetic during teeth extractions in 1844 but kept it a secret.
- ✓ Thomas Morton on October 16, 1846 demonstrated ether anaesthesia in public at an operation held at Massachusetts General Hospital. He was credited of being the first person to demonstrate the use of ether anaesthesia in public.
  He was also credited with the introduction of anaesthetic masks.
- ✓ The term anaesthesia, anaesthetic and the anaesthetist were coined by Oliver Wendel Holmes in 1846.
- ✓ John Snow devised an apparatus for controlling the administration of ether. He is also credited to classify the stages of anaesthesia.
  Chloroform anaesthesia became famous when John Snow was specially brought to London to induce its anaesthesia to Queen Victoria during the birth of her son Edward VII.
- ✓ Simpson recognized the advantages of chloroform over ether (rapid induction and less irritability to respiratory tract) and recommended it for all surgical procedures.

TYPES OF ANAESTHESIA:

(1) General Anaesthesia:

When there is loss of sensation of the whole body accompanied by loss of consciousness, it is called general anaesthesia, and the agents producing general anaesthesia are called general anaesthetics.

It may be produced by –

(i) Inhalation

(ii) the intravenous administration of non-volatile or non-gaseous anaesthetics (some may be given by intraperitoneal, intramuscular or other routes).

(iii) a combination of the above two with or without premedication.

(2) Regional Anaesthesia:

When there is loss of sensation of a large, but limited area of the body such as abdominal or pelvic region, it is called regional anaesthesia.

It may be produced by –

(i) perineural injection

(ii) spinal block: It can be produced by either epidural injection or intrathecal injection.

(3) Local Anaesthesia:

When there is loss of sensation of a particular small area of the body such as eye, horn base, limbs etc., it is called local anaesthesia and drugs used to produce local anaesthesia are called local anaesthetics.

It may be produced by –

(i) surface application

(ii) intra- and subdermal infiltration.

(iii) field analgesia – the blocking of an area by linear infiltration of its margins.

In both regional and local anaesthesia, the animal does not lose consciousness.

IMPORTANT TERMS:

Analgesia: It means loss of sensibility to pain. The drugs producing analgesia are called analgesics.

Tranquilization: It is a mild form of CNS depression producing a state of behavioural change in which the animal is relaxed and unconcerned with his surroundings. In this state, the animal is usually indifferent to minor pain but if pain is intense, the animal would not be relaxed. In terms of behavioural pharmacology, a state of tranquillization is the level of CNS depression just sufficient to produce loss of conditioned reflex. Agents producing a state of tranquillization are called tranquillizers or ataractics.

Sedation: It refers to a degree of CNS depression in which the patient is awake but calm and free from nervousness. The degree of CNS depression is higher than tranquillization but lower than hypnosis. A sedated buffalo would be indifferent to minor pain, more obliging and cooperative to physical restraint and may have slight ataxia. However, analgesia does not occur.

Hypnosis: It is depression of CNS equal to normal sleep. Drugs producing hypnosis are called hypnotics.

Narcotics: It is a state of drug induced sleep from which an animal can be aroused with great difficulty and into which it again relapses.

Preanaesthetic: Preanaesthetic (not necessarily a CNS depressant) is a drug which is administered before the administration of general anaesthetic to make the anaesthesia easy and safe. The administration of preanaesthetic suppresses bronchial, salivary, and lachrymal secretions. e.g. atropine.

Basal anaesthesia: Anaesthesia produced by preanaesthetic agents is called basal anaesthesia.

Balanced anaesthesia: An ideal anaesthetic should possess potent anaesthetic, adequate analgesic and sufficient muscle relaxant activities. Unfortunately, there is no single anaesthetic available which possesses all these qualities in adequate amount. Therefore, a combination of different drug substances such as anaesthetic, analgesic and muscle relaxant is prepared which gives the above mentioned activities. Such combination is known as balanced anaesthetic and the condition produced after its administration is called the balanced anaesthesia. Example – A combination of barbiturate (for CNS depression), pethidine (for analgesia) and d-tubocurarine (for muscle relaxation).

Dissociative anaesthesia: It is defined as the feeling of to be dissociated from or unaware of the environment during induction of anaesthesia.

Surgical anaesthesia: It is defined as the state where the animal is unconscious and unresponsive to painful surgical manipulations.

CHARACTERISTICS OF AN IDEAL GENERAL ANAESTHETIC AGENT:

(i) It should be easily and painlessly administered.
(ii) It should induce a rapid loss of consciousness without causing voluntary and involuntary struggling.
(iii) It should be non-toxic, non-irritant and non-explosive and stable during storage.
(iv) It should not cause physiological changes like drop in blood pressure, depression in respiration and heart action or increase in respiration or salivary secretion.
(v) It should give adequate analgesia and muscular relaxation at the minimum level of dosage required to cause loss of consciousness.
(vi) It should be easily neutralized by a non-toxic antidote, so that the duration of anaesthesia can be shortened at will.
(vii) It should have a short recovery period without excitement.
(viii) It should be compatible with premedication and other accessory therapeutics.
(ix) It should have a wide margin of safety.
(x) It should not promote capillary bleeding during surgery.
(xi) It should be easily available and inexpensive.

MECHANISM OF ACTION OF GENERAL ANAESTHETICS (Theories of General Anaesthesia):

Many theories have been given to explain the mechanism of action of general anaesthetics, but none of them is very satisfactory and no one explains the mechanism of action of all anaesthetic. The theories pertaining to mechanism of action of general anaesthetics are as follow:

(1) Colloidal theory:

This theory proposes that aggregation of colloids in cells accompanies anaesthesia reversibly and thereby allowing for recovery. Reversible cessation of protoplasmic streaming upon addition of chloroform, cyclopropane and ethyl chloride which is called “thexotropic sitting” inhibits movement of protoplasmic streaming and may cause depolymerization of microtubule structures that normally gives rigidity to cytoplasm.

(2) Lipid theory of Overton & Meyer (1901):

This theory proposes that there is direct relationship between affinity of an anaesthetic to lipids and its depressant action. Nerve cells and membranes contain lipids. The anaesthetic is thought to gain access to nerve tissue by virtue of its lipid solubility.

Now, we know that anaesthetics interact with proteins, so lipids become the site of localization or accumulation of the agents but not their mechanism of action.

(3) Surface tension or adsorption theory of Traube (1904):

Anaesthetics lower the surface tension. Narcotic agents accumulate at the cell surface that result in alteration of metabolic processes and neural transmission and that cause anaesthesia. These metabolic processes and neural transmissions may be due to changes in electric constant and permeability that may affect enzymes responsible for oxidative phosphorylation and electron transport. Nitrous oxide, cyclopropane, halothane and chloroform lower the surface tension of water-fat interface.

(4) Cell permeability theory:

Anaesthetics cause a change in permeability of cells in the CNS. Change in permeability interferes with the ionic movements necessary for membrane depolarization. Anaesthetic agents penetrate cell membrane and physically limit cell permeability and thus stabilize against depolarization (ether, chloroform and urathane). Diethylether selectively decreases the permeability to sodium ions. However, whether these changes cause anaesthesia and indeed, how these changes are produced remains unexplained.

(5) Biochemical theory:

Anaesthetic drugs act by modifying or interfering with the process of synthesis, storage, release, action and metabolism of one or more of the neurotransmitter agents. Uncoupling phosphorylation explains the mechanism of action of barbiturates and states that there is decreased synthesis of ATP due to inhibition of oxidative phosphorylation processes or enzymes by the anaesthetic drugs. The anaesthetic agents may inhibit the normal activity of one or more of the enzymes of CNS involved in the synthesis of certain neurotransmitter agents.

(6) Neurophysiological theory:

Anaesthetics inhibit ascending reticular formation which is important in maintenance of consciousness. Some anaesthetics such as cyclopropane have profound effect on diffuse thalamic projection system in brain while the subject remains quite aware of external stimuli. Thus, the theory gives important information regarding the neural effects of anaesthetics but does not propose a basic fundamental mechanism by which agents produce these effects.

(7) Physical theory or Microcrystal theory of Pauling and Miller (1961):

It deals with the molecular size of the agent which closes or interferes pores. Anaesthetics within the CNS are able to orient water molecules around them. This interaction with water (rather than lipid) results in formation of hydrated microcrystals or clathrates which interfere with neuronal excitability.

(8) Physiochemical theory:

Membrane has the primary site for anaesthetic action. Anaesthetics can expand the lipid phase of the membrane due to high hydrostatic pressure which can revert anaesthetic induced expansion of membrane, thus increasing fluidity or altering the shape of the pore within the membrane. These may cause changes in enzymatic activity. Also, this theory is not clear.

(9) Cell Membrane Expansion Theory or Protein Binding Theory of Frank & Lieb (1982):

The primary site of action of anaesthetic is either the lipid matrix of the biological membrane or hydrophobic regions of specific receptor proteins. Anaesthetics can bind to proteins presumably to hydrophobic sites. However, the absence of a satisfactory structure activity relationship for anaesthetic agents suggests that they do not produce their effects by specific interaction with a receptor protein. Thus, the most attractive possibility is that the primary action of anaesthetic is exerted on the lipid matrix of the biological membrane that results in local disordering of the lipid matrix which in turn inhibits the fluxes or ions which are responsible for neuronal excitability.

(10) Modern Molecular mechanism of action of general anaesthetics:

Most anaesthetics enhance the activity of inhibitory $GABA_A$ receptors, and many inhibit activation of excitatory receptors such as glutamate and nicotinic acetylcholine receptors.

At the cellular level, anaesthetic agents affect synaptic transmission rather than axonal conduction. The release of excitatory transmitters and the response of the post-synaptic receptors are both inhibited. GABA-mediated inhibitory transmission is enhanced by most anaesthetics.

$GABA_A$ receptors mediate anaesthesia of all halogenated anaesthetics (halothane, enflurane, isoflurane & sevoflurane) and some injectable anaesthetics like barbiturates, propofol, etomidate and neurosteroids. Glycine receptors mediate propofol, barbiturates and neurosteroid induced anaesthesia. NMDA (N-methyl-D-aspartate) receptors mediate anaesthesia of ketamine, N_2O and xenon.

Although, all parts of the nervous system are affected by anaesthetic agents, the main targets appear to be the thalamus, cortex and hippocampus.

[Controlling Centres: Mid-brain reticular formation - unconsciousness, thalamic sensory relay nuclei - analgesia, hippocampus - short term memory, spinal cord - reflexes]

SITE OF ACTION OF GENERAL ANAESTHETICS:

The general anaesthetic action is due to inhibition of ascending reticular activating system of reticular formation which normally maintains a state of wakefulness.

The depression of CNS progresses in the following order:

Cortex ⟶ Mid brain ⟶ Spinal cord ⟶ Medulla

STAGES OF ANAESTHESIA:

Dr. Guedel classified four stages of general anaesthesia:

[I]. Stage of voluntary excitement or stage of analgesia (Stage 1)
[II]. Stage of involuntary excitement or stage of delirium (Stage 2)
[III]. Stage of surgical anaesthesia (Stage 3)
[IV]. Stage of medullary paralysis or stage of respiratory arrest (Stage 4)

Stage 1 and stage 2 comprise **induction phase** of anaesthesia.

[I]. Stage of voluntary excitement or stage of analgesia:

- ✓ This stage begins from the beginning of the inhalation to loss of sensation.
- ✓ Excitement and struggling are the most characteristic features.
- ✓ Heart beat becomes faster and stronger and the respiration is rapid and deep.
- ✓ Pupil is dilated; there is excitement, and excessive salivation (due to irritation of vapour).
- ✓ There is analgesia without loss of consciousness.
- ✓ In horse, struggling is more violent and voluntary breath holding may occur.

[II]. Stage of Involuntary excitement or stage of delirium:

- ✓ This stage begins with depression of cortical centres with loss of consciousness and depression of voluntary centres.
- ✓ Apparent excitement is seen – patient may shout, struggle and hold his breath, muscle tone increases, jaws are tightly closed, breathing is jerky; vomiting, involuntary micturition or defaecation may occur.
- ✓ Heart rate and blood pressure may rise and pupils dilate due to sympathetic stimulation.
- ✓ In **horse**, **nystagamus** (oscillation of eye ball in the orbit) is characteristic of this stage but not in dog and other species.
- ✓ No stimulus should be applied or operative procedure carried out during this stage.
- ✓ This stage can be cut short by rapid induction, premedication etc. and is inconspicuous in modern anaesthesia.
- ✓ Stage 1 and 2 together is known as Induction Stage.

NB: Ether and chloroform induce all stages (i.e. 1, 2, 3 & 4) of anaesthesia and therefore called as **Totipotent anaesthetics** (that means 100% anaesthesia producing), whereas nitrous oxide and trichloroethylene do not produce stage 3 and 4 and therefore called as **Incomplete anaesthetics** (50% anaesthesia).

[III]. Stage of surgical anaesthesia:

- ✓ During this stage, depressant action of the anaesthetic is extended from the cortex and the mid brain to the spinal cord.

- ✓ Pain sensation, consciousness and spinal reflexes are abolished. Muscular relaxation occurs and coordinated movement disappears.
- ✓ Nearly all surgical procedures on animals are performed in this stage.

This stage is further subdivided into four planes i.e. plane 1, 2, 3 and 4. Plane 1 and 2 are collectively known as Light Surgical Anaesthesia. Plane 3 and 4 are known as Deep Surgical anaesthesia.

(i) Plane 1:

- Full, regular and automatic respiration – equally abdominal and thoracic.
- Roving eyeballs. This plane ends with eyes becoming fixed.

(ii) Plane 2:

- Regular but less exclusive respiration.
- Fixed eyeballs and starts dilating pupil in lower plane.
- All surgery is performed in 2nd plane of 3rd stage of anaesthesia except abdominal surgery (plane 3).

(iii)Plane 3:

- Increased abdominal respiration. Delayed thoracic respiration, starts paralysis of intercostals muscles.
- Pupil dilatation progresses and blood pressure starts falling.

(iv)Plane 4:

- Complete intercostal paralysis.
- Almost complete dilatation of pupil and light reflexes lost.
- Cessation of all respiratory efforts, leads 4th plane to 4th stage of anaesthesia.

[IV]. Stage of Medullary Paralysis or respiratory arrest:

- ✓ This stage starts from weakened respiratory efforts to complete heart failure.
- ✓ Vital medullary centres are paralyzed leading to respiratory failure and cardiac arrest.

***Clinical responses of the animal under general anaesthesia*:**

Stages of anaesthesia	Area of depression	Respirations	B.P.	Pulse	Reflexes						
					L	C	Sk	Sg	Cg	Pd	Ph
Voluntary excitement	Sensory cortex	Rapid & irregular	Rise	Rapid	+	+	+	+	+	+	+
Involuntary excitement	Motor cortex	Very irregular	Rise	Rapid	+	+	+	+	+	+	+
Surgical anaesthesia											
Plane 1	Mid-brain & sp. cord	Slow & regular	Normal	Normal	+	+	+	+	+	+	+
Plane 2	Spinal cord	Slow & regular	Normal	Normal	–	**+**	–	–	**+**	–	–
Plane 3	Spinal cord	Thoraco-abdominal	Fall	Rapid/weak	–	–	–	–	–	–	–
Plane 4	Slight medulla	Shallow abdominal	Fall	Rapid/weak	–	–	–	–	–	–	–
Medullary paralysis	Medulla	Absent	Fall	Feeble	–	–	–	–	–	–	–

+ present, – absent, L: Lid, C: Corneal, Sk: Skin, Sg: Swallowing, Cg: Cough, Pd: Pedal, Ph: Photomotor

GENERAL CONSIDERATIONS IN SELECTION OF ANAESTHETICS:

1. The anatomical and physiological peculiarities of the species and breed involved as well as the temperament and size of the animal influence the selection of anaesthetic agents.

   Dog & cat: (i) Ether with basal anaesthesia.
   (ii) Barbiturates (i.v.) preferred. {Barbiturates are not given in pregnant animals as barbiturates cause foetal asphyxia}.

   Horse: Chloroform as inhalant.
   Chloralhydras, magnesium sulphate and pentobarbitone sod. i.v.

   Swine: Pentobarbital sod. alongwith local and regional anaesthetics. General anaesthetics are not preferred due to obese characteristic of the animal.

2. The nature of operation performed, its size, duration and location are necessary considerations.

3. Species susceptibility: For example, opium and its derivatives are good in dog but should not be given to cat (Morphine contra-indicated in cat). Chloroform is not preferred in small animals.

4. Condition of the patient:
   (i) The animal should be fasted before being anaesthetized. But, there should not be prolonged fasting as it depletes glycogen reserve in the liver, thus, reducing the ability of that organ to detoxify poisons.
   (ii) Inhalation anaesthetics are not to be employed in respiratory diseases.
   (iii) Chloroform is not used in patients suffering from heart disorders.

CLASSIFICATION OF GENERAL ANAESTHETICS:

Based on route of administration, general anaesthetics amy be classified into two types:

(1) Inhalation Anaesthetics:

(i) Gaseous agents : Nitrous oxide and Cyclopropane.
(ii) Volatile liquids : Methoxyflurane, Halothane, Ether, Chloroform, Enflurane, Isoflurane, Desflurane, Sevoflurane etc.

(2) Parenteral Anaesthetics (Mostly intravenous):

Barbiturates: Pentobarbital, Thiopental, Thiamylal etc.
Non-Barbiturates: Chloralhydrate, Magnesium sulphate
Dissociative Anaesthetics: Ketamine
Steroid: Althesin
Neuroleptanalgesics: Droperidol, Fentanyl
Miscellaneous: Urethane, Chloralose, Metomidate, Etomidate, Propofol

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INHALATIONAL ANAESTHETICS

HISTORY OF INHALANT ANAESTHETICS:

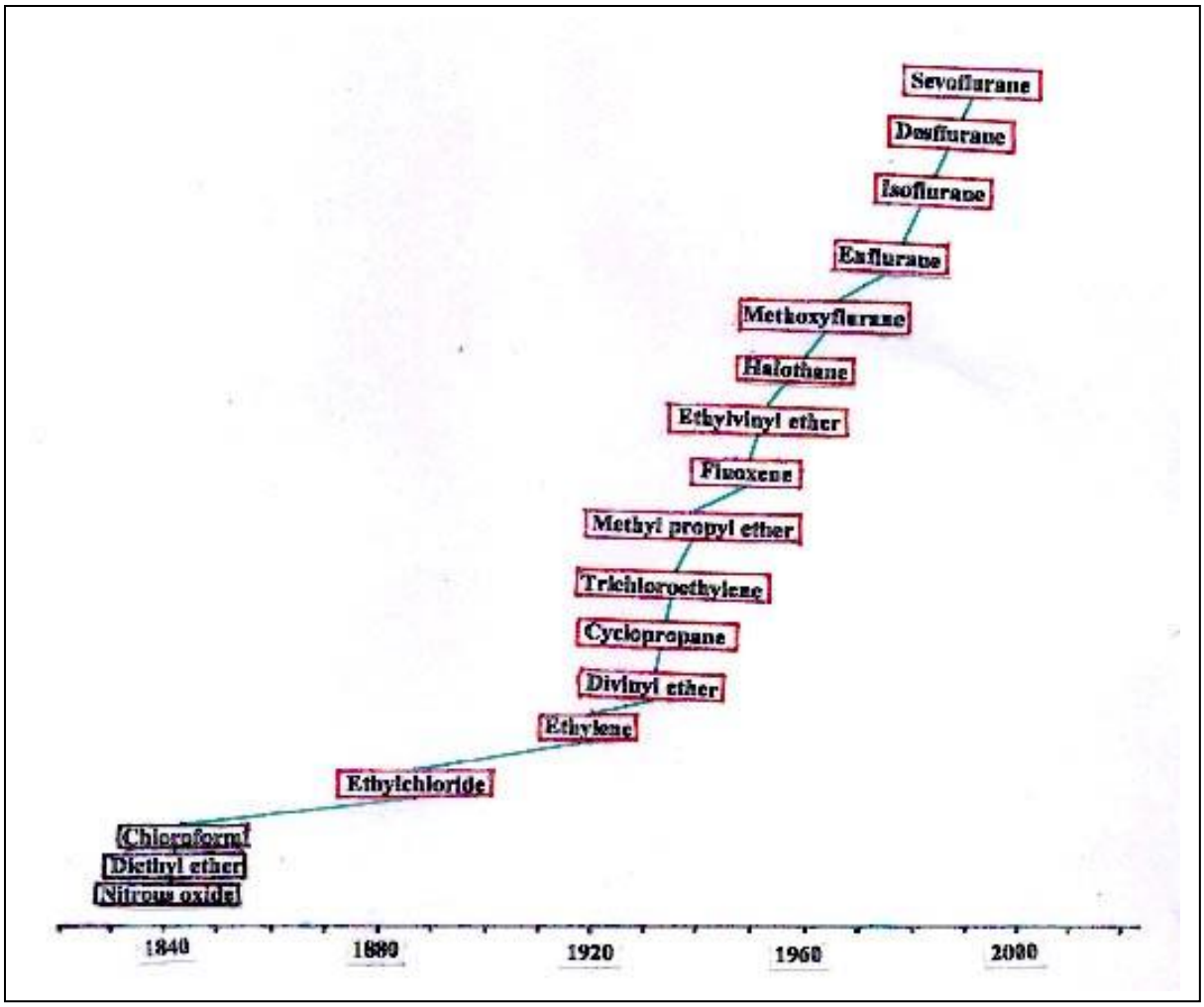


Fig.: Inhalational anaesthetics introduced for widespread clinical use.

GROUPS OF INHALANT ANAESTHETICS:

Group 1: Agents in current clinical use for animals.

Major use: Halothane, Isoflurane.

Minor use: Enflurane, methoxyflurane, nitrous oxide and diethyl ether.

Group 2: New agents. Examples: Desflurane and sevoflurane.

Group 3: Agents of historical interest. Examples: Chloroform, cyclopropane, fluoxene and trichloroethylene.

IMPORTANT TERMINOLOGY:

Minimum alveolar concentration (MAC):

It is the lowest concentration of the anaesthetic in pulmonary alveoli needed to produce immobility in response to a painful stimulus (surgical incision) in 50% individuals. Thus, MAC corresponds to Effective Dose - 50 or ED_{50}, i.e. half of the subjects anaesthetized and half are not. It is accepted as a standard index of anaesthetic potency for inhalational anaesthetics as it remains fairly constant for a given species even under varying conditions. It is expressed in percentage.

The anaesthetic potency of an inhaled anaesthetic is inversely related to MAC. Potency = 1/MAC; i.e. an agent having low anaesthetic potency will have a high MAC value and vice-versa.

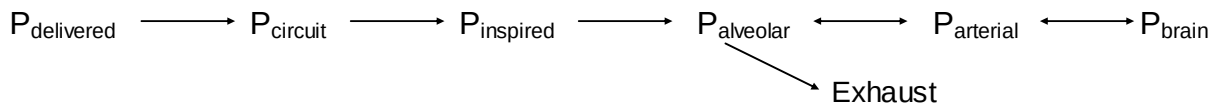
Solubility of Anaesthetics: It is determined by partition coefficients. Partition coefficient is the ratio of concentration of the agent in two phases at equilibrium.

Blood: gas partition coefficient: The blood/ gas solubility is a measure of the speed of anaesthetic induction, recovery and change of anaesthetic levels. Lower the blood/ gas partition coefficient, the more rapid the anaesthetic induction or rate of change of anaesthetic level in response to a stepwise change in anaesthetic delivery.

Oil: gas partition coefficient: A measure of fat solubility, determines the potency of an anaesthetic and also influences the kinetics of its distribution in the body, the main effect being that high lipid solubility delays recovery from anaesthesia.

PHARMACOKINETICS OF INHALATIONAL ANAESTHETICS:

Inhalational anaesthetics are gases or vapours that diffuse rapidly across pulmonary alveoli and tissue barriers. The depth of anaesthesia depends on the potency of the agent (MAC is an index of potency) and its partial pressure in the brain, while induction and recovery depend on the rate of change of partial pressure in the brain. Transfer of anaesthetic between lung and brain depends on a series of tension gradients which may be summarized as below –



- ☞ Rapid induction and recovery are important properties of an anaesthetic agent, allowing flexible control over the depth of anaesthesia.
- ☞ Speed of induction and recovery are determined by two properties of the anaesthetic i.e.
  - Solubility in blood (blood: gas partition coefficient), and
  - Solubility in fat i.e. lipid solubility (oil: gas partition coefficient).
- ☞ Agents with low blood: gas partition coefficient produce rapid induction and recovery (e.g. N_2O, Desflurane); agents with high blood:gas partition coefficients show slow induction and recovery (e.g. halothane).

- ☞ Agents with high lipid solubility (e.g. halothane) accumulate gradually in body fat and may produce a prolonged 'hangover' if used for a long operation.
- ☞ Some halogenated anaesthetics (e.g. halothane and methoxyflurane) are metabolized. This is not very important in determining their duration of action, but contributes to toxicity (e.g. renal toxicity associated with fluoride production with methoxyflurane – no longer used).

***Factors affecting the partial pressure of anaesthetic attained in brain are*:**

(i) Partial pressure of the anaesthetic in the inspired gas.
(ii) Pulmonary ventilation
(iii) Alveolar exchange
(iv) Solubility of the anaesthetic in blood – drugs with low solubility induce anaesthesia quickly.
(v) Solubility of the anaesthetic in tissue.
(vi) Cerebral blood flow.

***Elimination of inhalant anaesthetics*:**

When anaesthetic administration is discontinued, gradients are reversed and the channel of absorption (pulmonary epithelium) becomes the channel of elimination. Some factors which govern induction also govern recovery. Anaesthetics, in general, persist for longer periods in adipose tissue because of their high lipid solubility and low blood flow through fatty tissues. Muscles occupy an intermediate position between brain and adipose tissue. Most general anaesthetics are eliminated unchanged. Metabolism is significant only for halothane which is about 20% metabolized in liver. Others are practically not metabolized.

TECHNIQUES OF INHALATION OF ANAESTHETICS:

Different techniques are used according to facility available, agent used, condition of the patient, type and duration of operation.

(1) Open drop method:

Liquid anaesthetic is poured over a mask with gauge and its vapour is inhaled with air. A lot of anaesthetic vapour escapes in the surroundings and the concentration of the anaesthetic breathed by the patient can not be determined. It is wasteful – can be used only for cheap anaesthetics. Some rebreathing does occur in this method. However, it is simple and requires no special apparatus. Ether is the only agent used by this method.

(2) Through anaesthetic machines:

Use is made of gas cylinders, specialized graduated vaporizer, flow meters, unidirectional valves, corrugated rubber tubing and reservoir bag. The gases are delivered to the patient through a tightly fitting mask or endotracheal tube. Administration of the anaesthetic can be more precisely controlled and in many situations its concentration determined. Respiration can be controlled and assisted by the anaesthetist.

(a) Closed system
(b) Open system
(c) Semi-closed system.

ANAESTHETIC GASES

NITROUS OXIDE:

- It is a colourless, odourless, heavier than air, non-inflammable gas supplied under pressure in steel cylinders. It is non-irritating but low potency anaesthetic.
- The potency of nitrous oxide is poorest with a MAC value of 105% (man), 188% (dog), and 205% in cat, implying that even pure nitrous oxide can not produce adequate anaesthesia at atmospheric pressure.
- It induces only stage 1 & 2.
- It is a good analgesic, even 20% produces analgesia equivalent to that produced by conventional doses of morphine. It is a poor muscle relaxant.
- At least 20% O_2 in the inspired mixture is required to avoid **hypoxia** and for large animal species, inspired oxygen should not be less than 40%.
- Clinical uses: N_2O and O_2 can not be used alone in maintenance of anaesthesia. Therefore, N_2O is commonly used with preanaesthetic medication. N_2O (low potency), N_2O + O_2 + halothane (high potency) i.e. a triple mixture is used.
- Given for brief periods, N_2O is devoid of any serious toxic effects, but prolonged exposure (> 6 hrs) causes inactivation of *methionine synthase*, an enzyme required for DNA and protein synthesis, resulting in bone marrow depression that may cause leucopenia, so its use should be avoided in patients with anaemia related to vitamin B_{12} deficiency.
- N_2 tends to enter gaseous cavities in the body, causing them to expand. This can be dangerous if a pneumothorax or vascular air embolus is present, or if the intestine is obstructed.

CYCLOPROPANE: It is inflammable, explosive and costly gaseous anaesthetic. Also, it is a poor muscle relaxant. There is tendency of capillary oozing because of vasodilatation. Strongly depressant to respiration and hypotensive. So, it is less preferred now-a-days.

XENON: It is an inert gas shown many years ago to have anaesthetic properties, is making something of a comeback in the clinic because-not surprisingly for an inert gas-it lacks toxicity, but its relatively low potency and high cost are disadvantages.

VOLATILE LIQUIDS

ANAESTHETIC ETHER (Diethylether):

- It is highly volatile liquid, produces irritating vapours which are inflammable and explosive.
- Ether is oxidized to peroxide when exposed to air and moisture i.e. why 2% ethyl alcohol is added to convert toxic peroxides to acetaldehyde.
- Ether vapours upon ignition may cause explosion, hence never kept in refrigerator.
- It has excellent analgesic and muscle relaxant properties.
- It produces all stages of anaesthesia.
- There is slow induction and unpleasant vapours with struggling. There is salivation and marked respiratory secretion. So, atropine must be given as a premedicant.

CHLOROFORM:

- It is non-inflammable, non-explosive volatile liquid.
- The use of chloroform in modern anaesthetic practice is obsolete. It was used in horses and has been replaced by halothane, which is more safer.
- It is used to produce euthanasia for killing street dogs.
- It decomposes to phosgene gas on exposure to air, heat, or light which is very very irritant & toxic. Ethyl alcohol is added to chloroform to retard phosgene production.
- Chloroform is highly toxic to liver, heart & kidneys. It is converted to carbon tetrachloride in the liver.

HALOTHANE:

- It is a volatile liquid with sweet odour, non-irritating and non-inflammable.
- It is the most widely used inhalant anaesthetic in man and animals.
- Rapid induction (bypasses stage 2), smooth recovery, and potent anaesthetic only next to methoxyflurane and chloroform.

  Methoxyflurane (MAC 0.23%) > Chloroform (MAC 0.77%) > Halothane (MAC 0.87%).
- Halothane is not analgesic and has a relaxant effect on the uterus, which limits its usefulness for obstetric purposes.
- About 20% of the halothane is metabolized in the liver.
- It decomposes slowly on exposure to light to form volatile acids. So, 0.01% thymol is added as a stabilizer.
- Halothane is widely used inhalation anaesthetic but its use is now declining in favour of isoflurane and other drugs.
- Two rare bur serious adverse effects are associated with halothane are –
  - (i) Hepatotoxicity and
  - (ii) Malignant hyperthermia (genetic predisposition) – caused due to release of Ca^{2+} from the sarcoplasmic reticulum.

METHOXYFLURANE:

- It is non-inflammable, non-explosive volatile anaesthetic.
- It is the most potent (MAC value is 0.23%) inhalant anaesthetic.
- It causes excellent muscle relaxation and analgesia.
- Involuntary excitement is less (stage 2 bypassed).
- Slow induction and slow recovery, so some preanaesthetic or barbiturate should be given simultaneously for fast induction.
- It has potential renal toxicity and pronounced cardiopulmonary inhibition.

ENFLURANE:

- It is non-inflammable, non-irritating, new inhalant but convulsant anaesthetic.
- It is highly potent anaesthetic and structural analog of methoxyflurane.
- It causes CNS excitation causing twitching of facial, neck, limb and abdominal muscles. So, some anticonvulsants (like diazepam, ethosuximide etc.) should be administered before enflurane.

ISOFLURANE:

- Structural isomer of enflurane. It is non-toxic to liver and kidneys. It is not convulsant like enflurane. Anaesthetic potency is greater than enflurane.
- The drug has been approved by the FDA for anaesthesia in horse.
- Isoflurane is now the most widely used volatile anaesthetic.
- Expensive to manufacture because of its difficulty in separating isomers formed during synthesis.

DESFLURANE:

- Chemically similar to isoflurane, but its lower solubility in blood and fat means that inductions and recovery are faster, so it is increasingly used as an anaesthetic for day case surgery. It is not appreciably metabolized. It is less potent, MAC being about 6%.
- At concentrations used for induction (about 10%), desflurane causes some respiratory tract irritation, which can lead to coughing and bronchospasm.

SEVOFLURANE:

- It resembles desflurane but is more potent and does not cause respiratory irritation. It is partially (about 3%) metabolized, and detectable levels of fluorides are produced, although this does not appear to be sufficient to cause toxicity.

NB: Many inhalation anaesthetics have been introduced and gradually superseded, mainly because of their inflammable nature or because of toxicity. They include –

1. Chloroform: Hepatotoxicity and cardiac dysrhythmias.
2. Diethyl ether: Explosive and highly irritant to the respiratory tract leading to post-operative complications.
3. Vinyl ether: Explosive.
4. Cyclopropane: Explosive, strongly depressant to respiration and hypotensive.
5. Trichloroethylene: Chemically unstable, no special advantages.
6. Methoxyflurane: Slow recovery and renal toxicity.

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INTRAVENOUS ANAESTHETICS

Even the fastest-acting inhalation anaesthetics, such as **nitrous oxide**, take a few minutes to act and cause a period of excitement before anaesthesia is produced. Intravenous anaesthetics act much more rapidly, producing unconsciousness in about 20 seconds, as soon as the drug reaches the brain from its site of injection. These drugs (e.g. **thiopental, etomidate**, **propofol**) are normally used for induction of anaesthesia. They are preferred by patients because injection generally lacks the menacing quality associated with a face mask in an apprehensive individual.

Other drugs used as intravenous induction agents include certain benzodiazepines, such as **diazepam** and **midazolam**, which act rather less rapidly than the drugs listed above. Although intravenous anaesthetics on their own are generally unsatisfactory for producing maintained anaesthesia because their elimination from the body is relatively slow compared with that of inhalation agents, **propofol** can be used in this way, and the duration of action of **ketamine** is sufficient that it can be used for short operations without the need for an inhalation agent.

The combined use of **droperidol**, a dopamine antagonist related to antipsychotic drugs and an opiate analgesic such as **fentanyl** can produce a state of deep sedation and analgesia (known as *neuroleptanalgesia*) in which the patient remains responsive to simple commands and questions, but does not respond to painful stimuli or retain any memory of the procedure. This is used for minor procedures such as endoscopy.

Propanidid and **althesin** were withdrawn because of allergic reactions including hypotension and bronchoconstriction.

Advantages of Intravenous Anaesthetics:

1. It is easy to administer.
2. It directly produces stage III of surgical anaesthesia. Induction stages are bypassed.
3. It is safe for patients, veterinarian and the handlers.
4. It may be administered in the presence of diathermy or thermocautery.
5. Smooth induction and recovery (Horse may show some excitement).
6. Nausea and vomition are generally absent.
7. Post-anaesthetic period is free from complications.

Disadvantages of Intravenous anaesthetics:

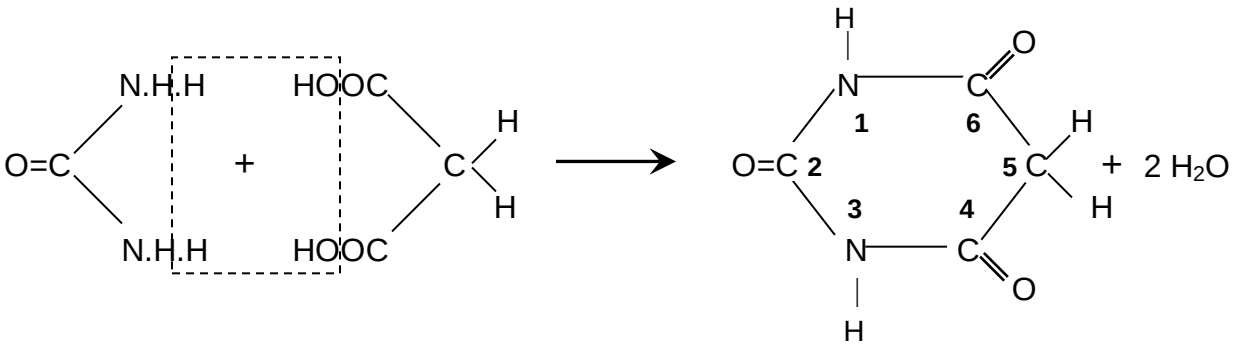
1. Depth and level of anaesthesia is not controlled.
2. The overdose can't be easily detoxified.
3. Muscle relaxation is not optimum.

CLASSIFICATION OF INTRAVENOUS ANAESTHETICS:

I. Barbiturates. Examples – Pentobarbitone Na (Nembutal®), Thiopental Na (Pentothal®), Thiamylal Na etc.
II. Non-barbiturates. Examples – Chloralhydrate, (Chloralhydrate+$MgSO_4$), (Chloralhydrate + $MgSO_4$ + Pentobarbitone Na).
III. Dissociative anaesthetics. Examples – Phencyclidine, Ketamine & Tiletamine.
IV. Steroid anaesthetics. Examples – Althesin.
V. Neuroleptanalgesics. Examples – Droperidol+Fentanyl, {Droperidol+Fentanyl +N_2O (66%)}
VI. Miscellaneous agents. Examples – Propofol, Etomidate, α-chloralose, Metomidate.

BARBITURATES

Barbiturates are derivatives of barbituric acid or malonyl urea. The basic compound barbituric acid is the condensation product urea and malonic acid, and consists of a six numbered ring structure.



Chemistry:

Barbiturates are bitter tasting white powders except for those containing sulphur. These may have a yellowish tint. Barbiturates are hygroscopic and will decompose on exposure on air, heat and light.

Barbiturates are derived from the non-depressant barbituric acid or malonyl urea which contains a pyrimidine nucleus. When the H atoms on C_5 are substituted with an appropriate alkyl or aryl group, depressant activity on the CNS is possessed by the compound.

Structure activity relationship (SAR):

(i) To be hypnotically effective, both H atoms on C_5 must be replaced by an alkyl or aryl group.
(ii) To obtain optimum therapeutic results, the substituting radicals on C_5 should contain a minimum of 4 and a maximum of 9 carbon atoms.
(iii) Unsaturated C-chains are more readily oxidized and hence short acting.
(iv) Short chains are more stable and hence long acting.
(v) Long chains are easily oxidized and hence short acting.
(vi) Branched chains are shorter acting than straight chains.
(vii) Only one aryl radical should be attached to C_5 position.
(viii) Replacement of O atom on C_2 by a S atom increases potency and also instability and thus shortens the duration of action of the compound.
(ix) Attachment of an alkyl group to one of the N atoms (i.e. position 1 & 3) increases anaesthetic potency and tends to stimulate the CNS. Substitution in both N atoms produces a convulsant.
(x) Replacement of O on C_2 by an =NH group destroys the hypnotic activity of the molecule.

Classification of barbiturates:

Category	Duration of action	Examples
Long acting	6 – 12 hours	Phenobarbital, Barbital
Intermediate acting	3 – 6 hours	Amobarbital, Pentobarbital
Short acting	1 – 3 hours	Secobarbital, Hexobarbital
Ultra-short acting	20 – 30 minutes	Thiopental, Thiamylal, Thialbarbital, Methohexital

Mechanism of action of barbiturates:

Barbiturates both enhance and mimic the action of γ-amino butyric acid (GABA), the principal inhibitory neurotransmitter in the CNS. Barbiturates depress the cortex of the brain and probably the thalamus. They depress the motor areas of the brain and the spinal cord and thus can be used to control convulsive seizures. They also depress sensory areas and induce anaesthesia. In clinical concentrations, barbiturates are the most potent known depressants of cerebral oxygen consumption.

Pharmacological actions of barbiturates on different body systems:

(i) *Cardiovascular system*: Slight decrease in blood pressure and heart rate.

(ii) *Respiratory centre*: Therapeutic doses of barbiturates depress respiration slightly (not in cat). Sub-anaesthetic doses of barbiturates increase respiration rate. Doses of barbiturates that induce deep surgical anaesthesia severely depress the respiration producing dangerous hypoxia and respiratory acidosis.

(iii) *Gastrointestinal tract*: Sedative doses of barbiturates do not affect the motility of gastrointestinal tract.

(iv) *Kidneys*: Hypnotic doses do not affect urine output. Anaesthetic doses cause decrease in glomerular filtration rate causing oliguria.

(v) *Liver*: Hepatic microsomal enzyme systems are activated at higher doses.

(vi) ***Uterus and foetus:*** Anaesthetic doses depress uterine contractions during parturition. The liver in newborn lacks the microsomal enzyme system required to biotransform or metabolize drugs such as barbiturates. Caesarean section performed solely under barbiturate anaesthesia will depress the foetus and may cause 100% foetal motility.

Clinical uses of barbiturates:

1. As an anaesthetic – Pentobarbital is used as an anaesthetic in dogs and cats.
   Dog – 24 to 33 mg/kg b.wt. i.v. in 3 – 6% aqueous solution.
   Cat – 25 mg/kg b.wt. i.v.
2. As anticonvulsant – Phenobarbital is used in epilepsy.
3. As sedative – Pentobarbital is used for sedation in foals and small colts. It can also be used as sedative in large animals (1 to 4.4 mg/kg b.wt. i.v.).
4. For euthanasia – Pentobarbital is generally used for euthanasia of small animals.
   Dose in dog – 40 to 60 mg/kg b.wt. i.v.

Intravenous anaesthetic doses of barbiturates in animals:

Barbiturate	Species	Dose (mg/kg)
Pentobarbitone (Nembutal Na®)	Dog & Cat Pig, Sheep & Goat	25 – 30 20 - 25
Thiopentone (Intraval Na®, Pentothal Na ®)	Dog & cat Pig Calf Horse Goat	15 – 30 5 – 10 15 – 20 10 15 – 20
Thiamylal	Dog, Cat & Pig Calf, Horse Goat	10 – 20 5 – 7 6 – 9
Methohexital	Dog, Cat, Pig & Horse	5 - 7

NB: *Half of the total calculated dose should be administered rapidly and the remainder to be injected slowly by observing the level of anaesthesia (i.e. to be injected according to the need).*

NON-BARBITURATES

CHLORAL HYDRATE:

- Chloral (trichloroacetaldehyde, $CCl_3.CHO$) is a non-selective C.N.S. depressant. On reaction with water, the crystalline solid, chloral hydrate, $CCl_3.CH(OH)_2$ is formed.
- It is the oldest of the injectable anaesthetics still in veterinary use. It was introduced in veterinary medicine by Humbert in 1875. He injected 30-70 g of chloral hydrate into horses. Since then it has been used to produce surgical anaesthesia in large animals especially horses.
- At low dose rates, chloral hydrate is a classical sedative, higher doses produce basal narcosis (a state of deep sedation bordering on general anaesthesia), and at high dose rates, general anaesthesia is obtained.
- It is reputed to have wide margin of safety.
- For large animals, relatively large volumes of dilute solutions are required and administration is slow. Stopping the i.v. infusion as soon as recumbency has induced ensures that overdosing does not occur.
- The slow onset of action of chloral hydrate is related not only to the slowness of administration but also to its fate in the body. It is a pro-drug. It is metabolized to trichloroethanol, which amounts for most of the pharmacological activity. Trichloroethanol is a liquid which is less convenient which is less convenient to use than chloral hydrate.

$CCl_3.CH(OH)_2$	$\longrightarrow$	$CCl_3.CH_2.OH$	$\longrightarrow$	$CCl_3.CH_2.OH$-glucuronide
Chloral hydrate		Trichloethanol		Urochloralic acid
Pro-drug		Active drug		Inactive metabolite

- Trichloroethanol is conjugated by liver microsomal enzymes with glucuronic acid. The glucuronide derivative, urochloralic acid, is inactive, polar and readily excreted.

Advantages of Chloral hydrate:

(i) Consistency of response (i.e. minimal interanimal variation).
(ii) Smooth induction and recovery in most animals.
(iii) Low cost.

Disadvantages of Chloral hydrate:

(i) Large volumes of solutions have to be administered, this is inconvenient and solutions must be freshly prepared.
(ii) Induction of anaesthesia is slow and can lead to practical difficulties of physical restraint before the animal becomes recumbent.
(iii) The depressant effects of chloral hydrate are slow to appear and it is difficult to assess the degree of ionization, which will ultimately be achieved as the drug is infused, since narcosis continues to deepen for several minutes after termination of the infusion.
(iv) A further potential hazard is the perivascular injection of chloral hydrate. It is an irritant drug and can cause tissue necrosis.
(v) Other side effects – depression of respiration and of cardiovascular system.

The current veterinary status of chloral hydrate is that of a drug which is declining in use, both as a sedative (oral administration) and general anaesthetic (i.v. administration). It is still used occasionally in horses and cattle, but not in other species.

Dank's Formulation [Chloral hydrate (12%) + $MgSO_4$ (6%)]:

$MgSO_4$ has got neuromuscular blocking activity, thus produces skeletal muscle relaxation. Chloralhydrate has got good hypnotic effect. So, the combination forms a satisfactory anaesthetic combination and has been used for anaesthesia in **horses** and **cattle**. The solution prepared should be used within an hour.

In camel, Chloralhydrate (12%) and $MgSO_4$ (12%) of each 6 gm/100 kg b.wt. is given i.v. for anaesthesia.

Millenbruck & Wallinega Formulation [Chloral hydrate + $MgSO_4$ + Pentobarbital Sodium]:

Good anaesthetic for horses and cattle. It is very cheap and consists of 30 gm Chloralhydrate, 15 gm $MgSO_4$ and 6.6 gm pentobarbital sodium dissolved in 1000 ml of water. Duration of anaesthesia is 30 minutes. Margin of safety is fair, recovery is satisfactory.

Dose – 30 – 70 ml/45 kg b.wt. i.v.

DISSOCIATIVE ANAESTHETICS

Phencyclidine HCl and its congeners Ketamine HCl and Tiletamine HCl are currently used as dissociative anaesthetic drugs in veterinary medicine. The term dissociative anaesthetic originated from the use of Ketamine in human medicine. Dissociative anaesthesia is defined as the feeling to be dissociated from or unaware of the environment during induction.

Phencyclidine is now a drug of abuse in man and has been banned in many countries.

Ketamine is now the most widely used dissociative anaesthetic in human and veterinary anesthesia.

KETAMINE:

It is a general anaesthetic which was first introduced in 1965 for use in humans. In 1970, it was introduced for anaesthesia in the cat. The important features of Ketamine are as below:

(i) It induces only stage I and II but not III & IV.
(ii) It does not act on ARS (Ascending Reticular System) like other general anaesthetics.
(iii) It produces depression of thalamoneocortical system and stimulation of limbic system. Therefore, due to dual action, Ketamine is called dissociative anaesthetic.
(iv) It induces anaesthesia and amnesia (loss of memory) by functional disruption (dissociation) of CNS through marked CNS excitation.
(v) It produces dissociation or complete unawareness of environment due to amnesia or forgetfulness.

Actions of Ketamine on Cardiovascular System (C.V.S.):

- ⋆ Ketamine increases cardiac output, blood pressure, central venous pressure and heart rate.
- ⋆ Cardiac stimulatory properties prove it a good induction agent for poor risk and hypovolemic patients.
- ⋆ It does not depress respiration, there is profound analgesia and amnesia, muscle relaxation is poor, induction rapid but recovery is prolonged. There is only little salivation which is not a problem, swallowing reflex is impaired.
- ⋆ It possesses wide margin of safety i.e. 5 times than that of Pentobarbitone.

Mechanism of action of Ketamine:

Ketamine inhibits a different type of ligand-gated ion channel, the *N*-methyl-D-aspartate (NMDA) receptor. NMDA receptors are glutamate-gated cation channels. Ketamine inhibits NMDA receptors by binding to the *phencyclidine* site on the NMDA-receptor protein, and the NMDA receptor is thought to be the principal molecular target for ketamine's anesthetic actions. Nitrous oxide, cyclopropane and xenon are potent and selective inhibitors of NMDA-activated currents, suggesting that these agents also may produce unconsciousness *via* actions on NMDA receptors.

Dose:

Ketamine is used with pre-medication of **xylazine** (in cat, cattle, sheep & horses), **detomidine** (in horses) and **azaperone** (in the pig).

Cat – Ketamine @ 44 mg/kg i.m. (Duration of anaesthesia 30-45 minutes).
Dog – Ketamine @ 10 mg/kg i.v. along with diazepam (@ 0.5 mg/kg i.v.).
Horse – Ketamine @ 2 mg/kg i.v. along with xylazine (@ 0.1 mg/kg i.v.).
Ketamine @ 2 mg/kg i.v. along with diazepam (@ 0.2 mg/kg i.v.).
Goat – Ketamine @ 10 mg/kg i.v. along with xylazine (@ 0.2 mg/kg i.v.).
Cattle – Ketamine @ 2 mg/kg i.v. rapidly.

TILETAMINE:

It is used with pre-medication of zolazepam (sheep, pigs, horses, dogs & cats).

STEROID ANAESTHETICS

The first injectable steroid anaesthetic was hydroxydione Na, but due to its unavoidable toxicity (i.e. very irritant & thrombophlebitis if injected perivascularly), its use was discontinued.

Alphaxalone + Alphadolone (Saffan or Althesin): Althesin is combination of two steroid drugs solubilized in an aqueous formulation containing polyethylated castor oil (Cremophor EL). Alphadolone has less anaesthetic activity than alphaxalone but is included to improve the solubility. The combination is a good anaesthetic, but contraindicated in dogs due to excessive histamine release from mast cells resulting in profound depression.

NEUROLEPT ANAESTHETICS

Fentanyl is a short acting (30-50 minutes), potent opioid analgesic while **droperidol** is a rapidly acting potent neuroleptic (antipsychotic). When a combination of these two is injected intravenously, a state of neurolept-analgesia is produced, characterized by general quiescence, psychic indifference and intense analgesia without unconsciousness. This state lasts for 30-40 minutes. Neurolept-analgesia is quite suitable for endoscopies, angiographies, burn dressings etc. and has been used for a variety of minor surgical procedures in severely ill or otherwise poor risk patients. The state of neurolept-analgesia can be converted to neurolept-anaesthesia by administering 65% N_2O + 35% O_2.

MISCELLANEOUS ANAESTHETICS

[I]. PROPOFOL: It resembles thiopentone in being highly lipid soluble (and thus producing anaesthesia in one vein-to-brain circulation time).

Advantages of Propofol:

- It is not painful after perivascular injection, does not cause irritation or inflammation.
- It is very rapidly metabolized, and because recovery does not depend on uptake by muscle or fat, it is non-cumulative. There is no hangover effect.
- There is excellent quality of anaesthesia produced – Induction, maintenance and recovery periods are smooth following single or incremental doses and after i.v. infusions.
- *It is the only intravenous anaesthetic that can be used for maintenance of general anaesthesia without the need of inhalant anaesthetics.*

Disadvantages of Propofol:

- Like barbiturates, equianaesthetic doses does produce similar degrees of C.V.S. and respiratory depression.

[II]. ETOMIDATE: It has gained favour over thiopental on account of the larger margin between the anaesthetic dose and the dose needed to produce respiratory and cardiovascular depression. It is also more rapidly metabolized than thiopental, and thus less likely to cause a prolonged hangover.

Disadvantages of Etomidate:

- Quality of anaesthesia – Poor. [Poor analgesic, muscle hypertonicity, tremor, involuntary muscle movements].
- Painful on injection to small veins.
- Etomidate is a potent inhibitor of Cyt. P_{450}-dependent 11-β-hydroxylase and an inhibitor of adrenal glucocorticoid synthesis. So, it should not be used in patients with adrenal insufficiency.

[III]. CHLORALOSE: It is the condensation product of anhydrous glucose and chloralhydrate. In body, it is converted to chloraldehyde which is further metabolized to trichloroethanol. It causes dissociative anaesthesia as Ketamine.

Dog – Chloralose @ 40-100 mg/kg i.v. followed by xylazine @ 1 mg/kg i.v.

[IV]. METOMIDATE: It is recommended for anaesthesia in birds. Also in pig, dog & cats.

COMPLICATIONS OF GENERAL ANAESTHESIA:

During anaesthesia:

- Respiratory depression
- Salivary, respiratory secretions
- Cardiac arrhythmia, asystole, Fall in blood pressure
- Aspiration of gastric contents, Laryngeospasm and asphyxia
- Delirium, convulsions
- Fire & explosion.

After anaesthesia:

- Nausea & vomiting, Pneumonia
- Persisting sedation, impaired psychomotor function
- Organ toxicities – liver, kidney damage.

PREANAESTHETIC MEDICATION

It consists of administration of certain drugs (for specific purpose so as to produce balanced anaesthesia) before general anaesthesia. The drugs generally used as preanaesthetics are sedatives, tranquillizers, analgesics, anticholinergics (muscarinic blockers) and muscle relaxants. They are administered about 30 minutes prior to induction of anaesthesia. The objectives of preanaesthetics medication include –

(i) To facilitate restraint of an excited or ferocious or uncooperative animal.
(ii) To help in smooth and rapid induction of anaesthesia and to result in smooth post-operative recovery.
(iii) To reduce the dose of the anaesthetic and thereby minimize its toxic effects.
(iv) To diminish salivation and bronchial secretions, esp. during inhalational anaesthesia.
(v) To prevent cardiac arrest following vagal stimulation.
(vi) To cause adequate skeletal muscle relaxation that is necessary for surgical operations.
(vii) To prevent vomition during induction or recovery.
(viii) To empty the gastrointestinal contents esp. before GI surgery.
(ix) Sometimes, before GI surgery, broad spectrum antibiotics are given so as to sterilize the GI tract.

Classification of Preanaesthetics:

1. Preanaesthetic skeletal muscle relaxants. Examples : d-tubocurarine, gallamine.
2. Preanaesthetic sedatives. Examples: Xylazine, meperidine (pethidine), diazepam, morphine, butorphanol.
3. Preanaesthetic sedative antiemetic. Examples: Acepromazine, chlorpromazine.
4. Preanaesthetics that diminish salivation and bronchial secretions esp. during inhalational anaesthesia and to prevent cardiac arrest. Examples: Atropine, glycopyrrolate.

POST-ANAESTHETIC MEDICATION

It consists of administration of certain drugs or other agents soon after surgery or during recovery. They are given to reduce the post-operative pain (analgesics), to calm down the animal when there is risk of injury to the blood during surgery (fluid/ electrolyte therapy or blood transfusion).

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Chapter - 3

Sedatives & Hypnotics

S E D A T I V E S

CLSSIFICATION OF SEDATIVES:

Primary classification	***Sub-classification***	***Examples***
Tranquillizer - sedatives	Phenothiazines	Promethazine, Promazine, Acepromazine, Chlorpromazine, Methotrimeprazine.
	Thioxanthines	Chloroprothixene
	Butyrophenones	Fluanisone, Azaperone, Droperidol
	Rauwolfia alkaloids	Reserpine
Sedative - hypnotics	Barbiturates	Phenobarbitone, Barbitone etc.
	Simple alcohols & aldehydes	– Chloralhydrate, Ethanol, Paraldehyde, Tribromoethanol
	Inorganic salts	Na bromide, Mag. sulphate
	Thiazines (α_2-agonists)	Xylazine, Detomidine, Clonidine Medetomidine.
	{α_2-antagonists	– Yohimbine, Idazoxan, Atipamezole}
	Benzodiazepines	Diazepam, Chlordiazepoxide, Zolazepam, Clonazepam.
	Purine-piperidines	Meprobamote.

Tranquillizer - sedatives (Tranquillizers, Ataractics or Neuroleptics):

These exert quietening, calming effects on animals, lessening anxiety and sometimes reducing fear and aggression in animal species with naturally vicious or nervous temperaments. They may be used to facilitate the handling of animals and as premedicants. Ataractics have similar uses to and some properties in common with sedative-hypnotics. There are, however, important differences in the pharmacological properties of these two type of drugs.

Sedative - hypnotics:

These are the drugs which depress the CNS sufficiently to cause lethargy, drowsiness and indifference to the surroundings. They decrease locomotor activity. They allay fear and apprehension, but the animal remains conscious, when the normal clinical dose rates are used. The term hypnotic implies loss of consciousness and is used here to indicate the effect of high doses, but clinically these drugs are usually used at sub-hypnotic dose rates. It is useful to distinguish these agents from the second group of sedatives (tranquillizer-sedatives) which do not produce loss of consciousness even at dose rates above the therapeutic range.

Difference between hypnotic-sedatives and tranquillizer sedatives:

Property	Hypnotic-sedative	Tranquillizer-sedative
1. Arousal reaction on sensory stimulation	Depressed	Can be normal or even exaggerated
2. Consistency of response (inter-animal variation)	Good	Often poor
3. Dose-effect relationship	Predictable and steep	Less predictable and flat
4. Effect of high dose rates	Loss of consciousness, anaethesia & respiratory depression	Consciousness retained with the animal in the state of cataleptic immobility. Minimal respiratory depression.
5. Safety margin	High only with normal sub-hypnotic doses	High
6. Effect on emesis	No effect or central stimulant action (xylazine)	Potent and specific depression of CTZ (chemoreceptor trigger zone) in medulla
7. Anticonvulsant actions	General (non-specific) for most drugs	More limited & specific
8. Premedication for anaesthesia	Duration not necessarily affected, suppression of recovery excitement may be limited.	More likely to prolong anaethesia & suppress recovery excitement.

INDIVIDUAL DRUGS:

1. Xylazine:

- ✓ Pharmacologically, xylazine is classified as an analgesic as well as a sedative and skeletal muscle relaxant. It is not a neuroleptic or tranquillizer nor an anaesthetic agent.
- ✓ Xylazine is a potent α_2-adrenergic agonist. Through its central stimulation of α_2-adrenergic receptors, xylazine has potent antinociceptive or analgesic activity.
- ✓ Because of direct stimulatory effect upon the emetic centre, emesis is commonly induced by xylazine in the cat and occasionally in the dog. The CTZ (chemoreceptor trigger zone) is activated by xylazine to trigger emesis (vomition).
- ✓ Ruminants are the most sensitive of the domestic animals to the action of xylazine. In cattle, doses that produce deep sedation and analgesia are $1/10^{th}$ those required in horses, dogs and cats.
- ✓ The pig is less effected by xylazine and doses levels are reported to be 20 – 30 times greater than those required in cattle. According to Benson & Thurmon (1979), xylazine is not effective in swine.
- ✓ Yohimbine, Idazoxan and Atipamezole are α_2-adrenergic antagonists. Yohimbine is generally used as α_2-antagonist. Idazoxan selectively antagonizes xylazine. Atipamezole selectively antagonizes medetomidine.

- ✓ Doses:

Animals	i.v. route (mg/kg)	i.m. route (mg/kg)
Horse	0.5 to 1.1	1 to 2
Cattle	0.03 to 0.1	0.1 to 0.2
Sheep	0.05 to 0.1	0.1 to 0.3
Goat	0.01 to 0.5	0.05 to 0.5
Pig	- - -	0.05 to 0.5
Dog & cat	0.5 to 1	1 to 2
Birds	0.5 to 1	5 to 10

2. Diazepam:

- ✓ It is the drug of choice for treating epilepsy in dog. Phenobarbitone is also used for treating epilepsy.
- ✓ It is also used as premedicant before ketamine anaesthesia.
- ✓ It acts by enhancing central inhibitory transmission processes mediated by GABA (GABA agonist).
- ✓ Dose in dog – 0.5 to 1.5 mg/kg.

3. Phenothiazines:

- ✓ These cause sedation and reduce spontaneous motor activity.
- ✓ Their mode of action is through antagonism of central neurotransmitter dopamine.
- ✓ Their anti-emetic effect is through inhibition of dopamine receptor in the CTZ (chemoreceptor trigger zone).
- ✓ Morphine induced CNS excitation in cat is blocked by these agents.
- ✓ These agents cause hypothermia due to depletion of catecholamines in hypothalamus.
- ✓ The phenothiazine derivatives are also weak anticholinergic, antihistaminic, antispasmodic, antiarrhythmic and curariform in property.

Dose:

(i) Chlorpromazine (Largactil®):

Dog & cat - 0.5 to 4 mg/kg i.v. as sedative and tranquillizer
1 to 6 mg/kg i.m. as sedative and tranquillizer
1 mg/kg i.m. as preanaesthetic

(NB: Chlorpromazine is not used in horses as it causes CNS excitation**)**

(ii) Triflupromazine (Siquil®):

Dog - 1 to 2 mg i.v. as tranquillizer
2 to 4 mg/kg i.m. as preanaesthetic
Cat - 4 to 8 mg/kg i.m. as preanaesthetic
Horse - 0.2 to 0.4 mg/kg i.v. as tranquillizer

4. Butyrophenones:

(i) Droperidol: It is the most potent anti-emetic known. It is used in combination with fentanyl as neuroleptanalgesic.
(ii) Haloperidol: It is used as anti-emetic in dog (0.05 to 0.1 mg/kg i.v. or i.m.).
(iii) Azaperone:It is used as tranquillizer in pig and horses.

[(NB:** Administration of catecholamines is contraindicated in animals pre-treated with phenothiazine or butyrophenone tranquillizers (due to hypotension produced by α-adrenergic receptor blockade.**)]

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Chapter - 4

Psychotropic Drugs

MOOD ELEVATORS

(**Antidepressants or Thymoleptics**)

Antidepressants or mood elevators (thymoleptics) are the drugs used for the treatment of affective disorders (depression and mania) in human subjects. The change of a mood of a person is characterized by either depression or mania. Sometimes both the conditions exist. Depression is characterized by feelings of sadness or misery, loss of concentration, disinterest of surroundings, loss of confidence, anorexia, insomnia or hypersomnia and lowered energy and libido. Severely depressed show tendency for suicide. Mania is characterized by excessive exuberance, enthusiasm & self confidence, easy irritability, hyperactivity and improper judgement.

The antidepressants are classified into four groups based on their chemical structure:

(1) **Tricyclic antidepressants**: e.g. Imipramine, desipramine, amitriptyline and protriptyline.

(2) **Monoamine oxidase (MAO) inhibitors**: e.g. Phenelzine, iproniazide, tranylcypramine and selegiline.

(3) **Heterogenous group (Atypical antidepressants)**: e.g. Mianserin, Nomifensine etc.

(4) Lithium carbonate.

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Chapter - 5

Analgesics

NARCOTIC ANALGESICS

Narcotic analgesics depress pain by their depressant actions on the CNS. Although, there are many drugs possessing central analgesic actions, the term narcotic analgesic or opioid receptor agonist is restricted to those which selectively produce analgesia without seriously impairing other functions, such as consciousness and sensory modalities other than pain. Hence, general depressants, such as general anaesthetics, are excluded from this definition.

OPIUM:

- ☞ It is the dried milky exudates produced by incision of the unripe seed capsules of the Oriental poppy plant, *Papaver somniferum*.
- ☞ Opium preparations have been employed in medicine for centuries for their sedative, euphoric and analgesic properties.
- ☞ Opium contains a number of pharmacologically active alkaloids.

Properties	Structure	Alkaloids	Total solids (%)
Analgesic & spasmogenic	Phenanthrene derivatives	Morphine Codeine Thebaine	10.0 0.5 0.2
Non-analgesic & spasmolytic	Benzylisoquinoline derivatives	Papaverine Narcotine Narceine	1.0 6.0 0.3

- ☞ **Papaverine** is a spasmolytic agent without significant actions on the CNS. **Narcotine** is a cough suppressant and **narceine** has little pharmacological activity. Only the phenanthrene alkaloids are analgesics.
- ☞ **Morphine** is the most potent analgesic constituent of opium, whilst **thebaine** has the weakest activity. The analgesic activity of opium is thus attributable almost entirely to morphine, since it is not only the most potent alkaloid but it is also present in the greatest quantity.
- ☞ Order of decreasing narcotic potency of phenanthrene alkaloids of opium is as follow: morphine > codeine > thebaine. This is also the order of increasing spinal stimulant activity. Thus thebaine causes violent convulsions, and practically devoid of analgesic and narcotic properties.

OPIOID RECEPTORS:

Classification of and drug action on opioid receptors:-

Receptor type	Physiological role
μ	Analgesia, indifference, cough suppression, respiratory depression, cardiovascular depression, physical dependence, hypothermia.
δ	Probably analgesia and indifference.
κ	Analgesia, sedation and ataxia.
σ	Euphoria or dysphoroa, hallucinations, excitement and probably analgesia.

Location of opioid receptors – Brain & spinal cord.

MORPHINE:

Analgesic actions of morphine:

- Of the several sub-types of opioid receptors, which have been classified above, it is the μ-receptor on which morphine and the related drugs fentanyl and pethidine, predominantly act.

  [NB: Endogenous opioid peptides like endorphins, enkephalins & dynorphin etc. are the naturally occurring analgesics in our body and work as analgesics. Another function of endogenous opioid peptides is regulation of feed intake**].**
- In providing relief from pain, narcotic analgesics act in two ways:-
  a. They raise the pain threshold, so that the pain is perceived only if the intensity of the pain stimulus is increased.
  b. They produce indifference to, or a greater tolerance of, pain that is perceived.
- The relief provided by morphine also depends on the type of pain: dull, prolonged pain being relieved more readily than sharp, acute pain.
- Normal consciousness is suppressed but it is normally possible to evoke an arousal response fairly readily. e.g. in noise.

Sedative, Excitatory & Addictive actions of morphine:

- In a number of species including man, dogs, monkeys, rats, rabbits and birds, morphine depresses the brain to produce a sedative action and at high dose levels, consciousness is lost.
- In the **cat**, there is an overall excitatory action rather than sedation. The response is profound and has been described as “maniacal excitement”. It has been attributed to the hypothalamic action of the drug.

  [NB: Even in the cat, it is now accepted that very low doses can produce analgesia without excitement**].**
- Other aspects of central effects of morphine include – tolerance and addiction.
- Addiction to morphine and similar compounds, notably heroin (diacetylmorphine), is a grave social problem in man.

  [NB: The addict becomes tolerant to many of the actions of morphine. For example – the lethal dose is greatly increased but there is less tolerance to the spasmogenic action on the gut and to the stimulant action on the nucleus of cranial nerve III. Consequently, the *morphine or heroin addict is characterized by* ***pin-point pupil*** *and by being* ***constipated.*****]**

Other actions of morphine:

- Morphine stimulates cranial nerve III in the mid-brain to produce miosis via the parasympathetic oculomotor nerve.
- Morphine depresses several centres in the medulla oblongata, including the vasomotor, cough and respiratory centres.
- Morphine stimulates the CTZ producing emesis.

- GIT – Morphine acts on the gut in two ways:-
  (i) Stimulates peristalsis via vagus nerve.
  (ii) Acts directly on the smooth muscles of the gut to cause a sustained, spasmodic contraction. It involves the sphincter muscles as well as the smooth muscles of the gut wall, inhibits effective peristaltic movements.

  The net result is – Initial defaecation followed by constipation.

Clinical uses of morphine:

In veterinary practice, morphine is used mainly in the dog:

(i) In any situation which requires the relief of pain.
(ii) For pre-medication prior to general anaesthesia.
(iii) Occasionally for treatment of diarrhoea.
(iv) Occasionally as a cough suppressant – For this purpose, newer drugs like butorphanol are preferred.

CODEINE:

- It has similar actions to morphine but is a less potent drug.
- It is used as the phosphate salt to relieve coughing in the dogs, and as analgesic and cough suppressant in the man.
- Addiction to codeine is uncommon.

DIAMORPHINE (Diacetylmorphine or Heroin):

- It is about 5 times as potent as morphine as an analgesic, narcotic and respiratory depressant.
- It is best known for its addictive properties in man.

METHADONE:

- It is a synthetic compound, approx. equipotent with morphine as an analgesic.
- It is a powerful **antitussives agent** and used in horses & dog for cough suppression.

PETHIDINE (Meperidine):

- It is about 1/10th as active as morphine as an analgesic.
- It is less likely than morphine to produce narcosis, vasodepression, emesis and depression of the medullary cough and respiratory centres.
- Thus, it is more suitable for use in dog and pregnant animals than morphine.
- So, pethidine is certainly suitable for routine use in these species.

APOMORPHINE:

- It is less potent than morphine as an analgesic and narcotic, but the central stimulant effects are increased.
- It is particularly potent as a centrally acting emetic acting as a stimulant on the CTZ of the medulla. It has been used as an emetic in the dog in cases of poisoning.

DEXTROMETHORPHAN:

- It lacks most of the properties of morphine including the analgesic, addictive, narcotic and spasmogenic actions.
- It does however, depresses the cough centre in the medulla and is used clinically as an antitussive in dogs when control of the dry productive cough is required.

ETORPHINE:

- It is a thebaine derivative.
- Its analgesic potency is 10,000 times the analgesic potency of morphine. The affinity of etorphine for opioid receptors is 20 times greater and its lipid solubility is 300 times greater than morphine so that it crosses blood brain barrier very rapidly and effectively.
- It is commonly used as a **capture drug** and it is generally recommended to dose heavily and then reverse as soon as possible with diprenorphine, the antagonist of etorphine.
- The potency of etorphine is extremely impressive.
- 1 mg (total dose) is capable of immobilizing a rhinoceros weighing approximately 2000 kg.
- A dose of 4 mg (total dose) is capable of immobilizing an African elephant weighing about 5000 kg.
- The lethal dose of etorphine for adult humans is very small. It is estimated to be 30-120 μg (total dose).
- *Uses*:
    (i) To immobilize game animals and as capture drug for wild animals.
    (ii) As narcotic analgesic in neuroleptanalgesia.

FENTANYL:

- It is approximately 50-100 times more potent than morphine as an analgesic.
- The main use of fentanyl is veterinary practice has been in neuroleptanalgesia.

AGONISTS AND ANTAGONISTS OF OPIOID RECEPTORS:

Opioid agonists	**Opioid antagonists**	**Partial opioid agonists**	**Opioid agonist - antagonist (Mixed agonist - antagonist)**
Morphine	Naloxone	Buprenorphine	Nalbuphine
Codeine	Diprenorphine	Tramadol	Pentazocine
Hydromorphone	Naltrexone		Butorphanol
Oxymorphone	Nalmefene		Nalorphine
Meperidine			
Methadone			
Fentanyl			
Etorphine			

Drugs activity on opioid receptors can be regarded as falling on a continuous scale ranging from pure agonists to pure antagonists:-

1. Strong agonist – Phenazocine
2. Agonist – Morphine
3. Weak agonist – Methadone
4. Mixed agonist-antagonist (Partial agonist) – Pentazocine, Buprenorphine & butorphanol
5. Antagonist with slight agonistic activity – Nalorphine & Diprenorphine
6. Pure antagonist – Naloxone, Naltrexone.

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NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

All drugs grouped in this class have analgesic, antipyretic and anti-inflammatory actions in different measures. Compared to morphine they are weaker analgesics (except for inflammatory pain); do not depress CNS, do not produce physical dependence and have no abuse liability. They are also called **non-narcotic, non-opioid** or **aspirin like analgesics**. They act primarily on peripheral pain mechanisms but also in CNS to raise pain threshold.

Classification of NSAIDs based on chemical groupings:

1. *Salicylates:* Sodium salicylate, Acetylsalicylic acid (aspirin), Methylsalicylate.
2. *Aniline or p-aminophenol derivatives***:** Paracetamol (acetaminophen), Acetanilide, Phenacetin, Aminopyrine, Antipyrine.
3. *Pyrazolone derivatives:* Phenylbutazone, Oxyphenbutazone, Sulphinpyrazone.
4. *Indole & related drugs:* Indomethacin, Sulindac.
5. *Phenyl acetic acid derivatives:* Diclofenac.
6. *Propionic acid derivatives:* Ibuprofen, Naproxen, Fenoprofen, Ketoprofen.
7. *Fenamates:* Mefenamic acid.
8. *Oxicams:* Piroxicam, Tenoxicam, Meloxicam.
9. *Sulfonanilide derivatives:* Nimesulide.

Classification of NSAIDs based on selectivity of COX Inhibition:

A. *Non-selective COX Inhibitors (Conventional NSAIDs):*
   1. Salicylates: Aspirin, Diflunisal.
   2. Pyrazolone derivatives: Phenylbutazone, Oxyphenbutazone.
   3. Indole derivatives: Indomethacin.
   4. Propionic acid derivatives: Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen.
   5. Anthranilic acid derivatives: Mefenamic acid.
   6. Aryl acetic acid derivatives: Diclofenac.
   7. Oxicam derivatives: Piroxicam, Tenoxicam.
   8. Pyrrolo-pyrrole derivatives: Ketorolac.

B. *Preferential COX-2 Inhibitors:* Nimesulide, Meloxicam, Nabumetone.

C. *Selective COX-2 Inhibitors:* Celecoxib, Rofecoxib, Valdecoxib.

D. *Analgesic-antipyretic with poor anti-inflammatory action:*
   1. p-aminophenol derivatives: Paracetamol (Acetaminophen).
   2. Pyrazolone derivatives: Metamizol.
   3. Benzoxacine derivatives: Nefopam.

MECHANISM OF ACTION OF NSAIDs:

NSAIDs block the enzyme cyclo-oxygenase (COX), so block prostaglandin (PG) synthesis and ultimately inflammation.

Beneficial actions of PG synthesis inhibition: Analgesia, antipyresis, anti-inflammatory action and antithrombotic action.

Shared toxicities due to PG synthesis inhibition:

- Gastric irritation which may range from simple discomfort to ulcer formation,
- Limitation of renal blood flow (due to Na^+ and water retention),
- A tendency to prolong bleeding (due to inhibition of platelet function),
- Delayed/ prolongation of labour,
- Asthma and anaphylactoid reactions in susceptible individuals.

***Analgesia*:** Prostaglandins induce hyperalgesia, i.e. why NSAIDs are effective only against pain associated with inflammation.

***Antipyresis*:** NSAIDs reduce body temperature in fever but do not cause hypothermia in normothermic individuals. Fever during infection is produced through generation of pyrogen which induces PG production in hypothalamus which raises its temperature set point.

***Anti-inflammatory action*:** PGs cause vasodilatation & exudation resulting in inflammation. NSAIDs inhibit PG synthesis at the site of injury.

***Dysmenorrhoea*:** Involvement of PGs in dysmenorrhoea has been clearly demonstrated. Level of PGs in menstrual outflow is increased in dysmenorrhoeic women. NSAIDs lower uterine PG levels – affords excellent relief in 60-70% and partial relief in the remaining.

***Anti-platelet aggregatory action*:** Thromboxanes help in aggregation of platelets. NSAIDs inhibit platelet aggregation by inhibiting synthesis of thromboxanes mediated via COX. Aspirin is highly active.

***Parturition*:** Sudden spurt of PG synthesis by uterus triggers labour and facilitates its progression. Accordingly, NSAIDs have the potential to delay & retard labour.

***Gastric mucosal damage*:** Gastric pain, mucosal erosion/ ulceration and blood loss are produced by all NSAIDs to varying extents: relative gastric toxicity is a major consideration in the choice of NSAIDs. Inhibition of the synthesis of gastro-protective PGs (PgE_2, PGI_2 etc.) is clearly involved; though local actions inducing back diffusion of H^+ in gastric mucosa also plays a role. Paracetamol, a very weak inhibitor of COX is practically free of gastric toxicity. Selective COX-2 inhibitors are safer.

ANTIPYRETIC EFFECTS OF NSAIDs:

Normal body temperature (thermostat) is maintained by the thermoregulatory centre located in the hypothalamus. Fever occurs due to disturbance in hypothalamic thermostat, which is set at a higher temperature. During infections and inflammatory reactions, the pathogenic microbial endotoxins cause release of pyrogen Interleukin-1 from neutrophils and macrophages, which stimulate the generation of prostaglandins (E series) in the hypothalamus which set the thermostat at a higher level, resulting in pyrexia or fever.

The antipyretics act by resetting the thermostat to normal set point and then the body temperature regulating mechanisms (like dilatation of superficial blood vessels, sweating and increased respiration promoting heat loss) operate to lower the elevated body temperature to normal level. NSAIDs also exert their antipyretic effect by irreversibly inhibiting their cyclo-oxygenase production from arachiodonic acid in the hypothalamus. Normal body temperature is not affected by NSAIDs or antipyretics (at therapeutic dosage).

ANALGESIC EFFECTS OF NSAIDs:

Prostaglandins induce hyperalgesia/ hyperaesthesia due to sensitization of nociceptors to pain. That is, why, NSAIDs are effective only against pain associated with inflammation (like arthritis, bursitis, muscular pain, vascular pain, toothache, dysmenorrhoea and bone pain). NSAIDs exert analgesic effect by inhibiting prostaglandin synthesis through irreversible inhibition of cyclo-oxygenase.

ANTI-INFLAMMATORY EFFECTS OF NSAIDs:

The inflammatory reactions such as vasodilatation increased vascular permeability, cell proliferation, pain etc. are mediated by release of multitude of chemical mediators having varied mechanisms of action. These mediators further induce synthesis of prostaglandins through cyclo-oxygenase which ultimately produce inflammation. NSAIDs exert anti-inflammatory effect by inhibition of prostaglandin synthesis through cyclo-oxygenase -2. Aspirin in addition to the above effects also prolongs clotting time by preventing platelet aggregation (by inhibiting thromboxane A_2 synthesis in platelets). So, also used for the treatment of coronary blocks, myocardial infarction and angina

Table: A comparison of the spectrum of action of NSAIDs of veterinary interest; sulphinpyrazone and glucocorticoids are included for completeness.

NSAIDs & others	Central analgesic	Antipyretic	Anti-inflammatory	Uricosuric
Aspirin	+	+	+	±
Paracetamol	+	+	0	0
Phenylbutazone	0	±	+	+
Sulphinpyrazone	0	0	0	+
Meclofenamate	0	+	+	NA
Naproxen	0	+	+	NA
Flunixin	+	+	+	NA
Glucocorticoids	0	0	+	Inhibits

Relative Potency of NSAIDs:

Antipyretic Effect: Aspirin = Paracetamol > Phenacetin > Phenylbutazone

Analgesic Effect: Aspirin > Phenacetin & Paracetamol > Phenylbutazone

Anti-inflammatory Effect: Phenylbutazone > Aspirin

SALICYLATES: Salicylates generally act by virtue of their content of salicylic acid which is responsible for most of the actions.

1. **Salicylic acid:** Salicylic acid (orthohydroxybenzoic acid) is so irritating that it can only be used externally; therefore various derivatives of this acid have been synthesized for systemic use. It is confined to external use only as a keratolytic agent.
2. **Methylsalicylate:** It is a component of liniments and ointments with rubefacient action.
3. **Sodium salicylate:** It is the active ingredient of oral febrifuge prescriptions in veterinary practice. The drug is freely soluble in water and is rapidly absorbed from GI tract.

4. **Aspirin (Acetylsalicylic acid):** It is rapidly converted in the body to salicylic acid which is responsible for most of the actions of aspirin. It is one of the oldest analgesic-anti-inflammatory drugs and is still widely used. More potent than sodium salicylate but less soluble.

ANILINE DERIVATIVES (p-aminophenol derivatives):
[Acetanilide, Phenacetin & Paracetamol (or Acetaminophen)]

- The members of the family are less irritant to the stomach than salicylates and lack the anti-inflammatory potency of salicylates, but they are equipotent as antipyretic analgesics.
- These members (acetanilide, phenacetin and paracetamol) acting via metabolites oxidize Hb to Met Hb and Sulph Hb, shortens the life of erythrocytes and can cause frank haemolysis. Paracetamol is the least toxic member of the family. It is free of all the side effects and adverse reactions of aspirin, and excreted as conjugates in urine.
- There may be poisoning by paracetamol (in overdose) in **cats**. Methionine and cysteine are glutathione precursors and have antidotal value in paracetamol poisoning.

PYRAZOLONE DERIVATIVES:

- Previously *antipyrine* (phenazone) and *amidopyrine* (aminopyrine) were introduced as antipyretics and analgesics. Their use was associated with high incidence of agranulocytosis, hypersensitivity reactions, tremors, sweating etc. That is, why, these drugs were banned in many countries including India.
- **Phenylbutazone** and its active metabolite oxyphenbutazone (less active than phenylbutazone) have potent anti-inflammatory actions rather than analgesic properties. These are also rarely used now, due to residual risk of bone marrow depression and other toxicities in human beings but used in horses and dogs. In horses (doping agent), phenylbutazone is widely used to treat to give symptomatic relief from muscle, bone and joint lesions in horses. The detection of phenylbutazone or its longer lived metabolite oxyphenbutazone in race horse urine samples has given rise to the so-called **"8-day rule"**, 8 days being suggested minimum period between the last treatment and racing to ensure a negative urine test.
- Other pyrazolones used safely are **metamizol** and **propiphenazole** used as analgesic and antipyretic.
- **Sulphinpyrazone** – It is a uricosuric agent (unusual among NSAIDs) with no anti-inflammatory property.

INDOMETHACIN:

- It is a more powerful anti-inflammatory drug and most potent inhibitor of cyclo-oxygenase *in vitro*.
- Due to this action, it can extend the duration of pregnancy in experimental animals.
- It also inhibits the diuretic potency of furosemide.
- Side effects – headache, diarrhoea, blood dyscrasias, ulcers in GIT etc.

DICLOFENAC:

- Analgesic, antipyretic & anti-inflammatory drug.
- It is among the most extensively used NSAIDs employed in rheumatoid and osteoarthritis, bursitis, ankylosing spondylitis, dysmenorrhoea, post-traumatic

and post-operative inflammatory conditions – affords quick relief of pain and wound oedema.
- Side effects are generally mild.
- Now-a-days, banned for veterinary practice in India due to mortality of vultures scavenging on carcasses of animals containing residues of diclofenac. In poultry, diclofenac causes gout and other pathogenic lesions which result in their mortality.

PROPIONIC ACID DERIVATIVES:

1. **Ibuprofen:** It is popular drug in human medicine because its use is associated with a low incidence of GI side effects. However, GI erosions consistently occur in dogs (hence, not recommended for use in dogs).
2. **Ketoprofen:** It is a strong inhibitor of cyclo-oxygenase; hence it has powerful anti-inflammatory, analgesic and anti-pyretic properties (Effective in rheumatoid arthritis & post-operative pain control). It is relatively safer.
3. **Naproxen:** It has analgesic, antipyretic and anti-inflammatory effects. In horses, it can be effectively used for myositis bringing complete relief from pain and lameness in 5 to 6 days. The drug is toxic in dogs. In human beings, the drug produces less GI damage than aspirin.

FENAMATES:

- It has antipyretic, analgesics and anti-inflammatory potency.
- The analgesic is secondary to anti-inflammatory effect.
- Meclofenamic acid is noted for its slow onset of action. It is an antagonist of $PGF_{2\alpha}$ and can protect against bovine experimental anaphylaxis.

OXICAMS:

1. **Piroxicam:** It is a good analgesic, antipyretic and anti-inflammatory agent. It is suited for use as short term analgesic and long term anti-inflammatory drug – rheumatoid and osteoarthritis, ankylosing spondylitis, acute gout, musculoskeletal injuries, dentistry, episiotomy, dysmenorrhoea etc.
2. **Meloxicam:** It has 10-14 folds COX-2 selectivity than COX-1. So, it has been labeled “preferential COX-2 Inhibitor”. Efficacy of meloxicam in osteoarthritis & rheumatoid arthritis is comparable to piroxicam. Gastric side effects are milder.

NIMESULIDE:

- Relative COX-2 selectivity.
- Weak inhibitor of PG synthesis.
- Analgesic, anti-pyretic and anti-inflammatory activity of Nimesulide is comparable to other NSAIDs.

NEWER AGENTS:

1. **Celecoxib:** 6-375 fold COX-2 selectivity. Good anti-inflammatory, analgesic, antipyretic and low ulcerogenic properties.
2. **Valdecoxib:** 10 -100 fold COX-2 selectivity.
3. **Rofecoxib:** 100 - 1000 fold COX-2 selectivity.

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Chapter - 6

C.N.S. Stimulants

C. N. S. STIMULANTS

These are the drugs which counteract the excess CNS depression that is commonly associated with the overdosage of anaesthtics and in toxicity of certain drugs or poisonings. Death in excess CNS depression results either from respiratory or cardiac failure or both. The CNS stimulants act by stimulating the respiratory and/or vasomotor centres. Overdosage of CNS stimulants results in convulsive attacks, which can be countered by the administration of CNS depressants (hypnotics, anticonvulsants etc.).

Classification of CNS stimulants:

1. Cortical stimulants: These are further sub-divided on the basis of the nature of their action into three types:
   (a) *Classical cortical stimulants*: e.g. Cocaine, Amphetamine, Ephedrine, Xanthines (Caffeine, Theophylline and Theobromide).
   (b) *Psychotomimetics* (Hallucinogens): e.g. LSD, Mescaline.
   (c) *Antidepressants* (Thymoleptics or mood elevators): e.g. Imipramine, Iproniazid, Tranylcypramine etc.
2. Medullary stimulants (Analeptics): e.g. Bemegride, Leptazol, Nikethamide, Picrotoxin, Doxapram.
3. Spinal stimulants: e.g. Strychnine, Brucine, picrotoxin etc.

Importance of CNS stimulants:

(ii) Some are employed clinically in man to treat states of mental depression {i.e. mainly group 1(a)}.

(iii) Some (principally group 2 or analeptics) are used clinically in animals to stimulate the CNS, following overdosage with centrally acting depressants, usually injectable anaesthetics (an example of physiological antagonism).

(iv) Some are of social significance to man, since they have become drugs of addiction {mainly group 1(b)}.

(v) Others have few clinical uses in either animals or man, but have been used to study central mechanisms or synaptic transmission (e.g. group 3).

(vi) Drugs in group 3 have been used as animal poisons and accidental poisoning of domestic animals can occur; and

(vii) One group of cortical stimulants, the xanthines, are used clinically for their cardiovascular and diuretic actions, and CNS stimulation may be an important, unwanted side effect.

INDIVIDUAL DRUGS:

1. **Strychnine:** It is obtained from the seeds of *Strychnos nuxvomica*. It stimulates all parts of the CNS causing violent **convulsions**. It increases the neuronal activity by selectively blocking the central inhibitory (post-synaptic) processes that are mediated by glycine. Strychnine is a competitive antagonist of glycine receptors at motoneurons and interneurons in the spinal cord.

2. **Picrotoxin:** It is a non-nitrogenous substance obtained from the seeds of *Amanita cocculus.* It is a potent **convulsive** agent that acts by selectively inhibiting the central inhibitory processes (presynaptic) that are mediated by GABA in brainstem and in spinal cord.
3. **Nikethamide (Coramine):** It is chemically related to nicotinamide and therefore has a mild antipellegra activity. Nikethamide is mainly a **respiratory stimulant** and acts by indirectly stimulating the medullary respiratory cenre through increased activity of chemoreceptors in the carotid and aortic bodies.
   Dose: Dog – 20 to 40 mg/kg i.v. or i.m., repeat if needed within 15-20 minutes.
4. **Amphetamine:** It is a sympathomimetic drug having marked CNS stimulant property. It produces an arousal reaction in animals under anaesthesia. It directly stimulates the respiratory centre and dilates the bronchi through sympathetic activity.
5. **Doxapram:** It is primarily a **respiratory stimulant** through both direct and indirect actions i.e. direct by stimulating medullary centre and indirect through increased chemoreceptor activity. Doxapram also has pressure effect which may be through stimulation of sympathetic outflow. It is mainly used to relieve anaesthetic respiratory depression.
6. **Xanthine derivatives:**
   (a) Caffeine: It stimulates cerebral (sensory) cortex. It has a direct stimulant effect on the depressed respiratory centre. It also increases the sensitivity of the respiratory centre to CO_2. It has diuretic effect by antagonizing the effect of ADH.
   (b) Aminophylline: Its actions are nearly similar to caffeine. It also relieves bronchial spasm through presynaptic antagonism of adenosine as caffeine.
7. **Bemegride:** It is a direct stimulant of depressed respiratory centre and a specific antagonist of barbiturates. Dose in dog – 15 to 20 mg/kg i.v.

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Chapter - 7

Drugs acting on Somatic Nervous System

LOCAL ANAESTHETICS

Local anaesthetics are drugs which cause reversible loss of sensation of a particular area or region of the body. The effect is not accompanied by loss of consciousness. The local anaesthetic solutions are injected near or in vicinity of the nerves and applied topically for localized desensitization.

MECHANISM OF ACTION OF LOCAL ANAESTHETICS:

Following injection of these agents into tissue spaces, the free amine or alkaloidal base is released, which readily penetrates into the lipid neuronal membrane. The local anaesthetics prevent depolarization of the neurons by interfering with Na^+ ion permeability resulting in blockade of impulse conduction. This effect is due to reversible binding to the Na^+ ion channels in the neuronal membrane.

DIFFERENTIAL FEATURES OF LOCAL AND GENERAL ANAESTHETICS:

Parameters	Local anaesthetics	General anaesthetics
1. Site of action	PNS: Peripheral nerves	CNS: Brain
2. Mode of action	Blocks axonal conduction	Alters synaptic transmission
3. Consciousness	Unaffected	Lost
4. Analgesia	Localized	Generalized
5. Administration	Local deposition away from systemic circulation	Systemic – Inhalation or parenteral
6. Systemic availability	Undesirable, responsible for toxicity	Requisite for action
7. Toxic potential & toxicity	Low, CNS stimulation (convulsive seizures)	High, CNS depression

SYSTEMIC EFFECTS OF LOCAL ANAESTHETICS (Toxicity):

Following absorption in significant quantities from the site of administration, they may cause CNS excitation (restlessness, tremors and even convulsions), neuromuscular & ganglionic blockade, myocardial depression and antispasmodic effect on intestinal smooth muscles.

Antidotal measures include a short acting barbiturate or diazepam to control convulsions; and the provision of oxygen or artificial respiration in the event of respiratory embarrassment or depression.

PROPERTIES OF AN IDEAL LOCAL ANAESTHETIC AGENT:

(i) It should provide reversible sensory nerve blockade with no local (e.g. neural) or systemic (e.g. CNS or cardiac) toxicity.
(ii) The onset and duration of blockade should be predictable and consistent in all applications.
(iii) It should have negligible irritancy to tissues at therapeutic concentrations.
(iv) It should be slowly absorbed into the systemic circulation from the site of administration so that its action is prolonged and systemic toxicity is minimized.
(v) Once absorbed into systemic circulation, it should be rapidly detoxified.

CLASSIFICATION OF LOCAL ANAESTHETICS:

Categories	Duration of action	Examples
1. Ultra-short acting	Less than or equal to 15 min.	Proparacaine Benoxinate
2. Short acting	Approx. 1 hour	Procaine Chlorprocaine Cocaine
3. Intermediate acting	1 – 4 hour	Lidocaine (Xylocaine) Mepivacaine Prilocaine
4. Long acting	4 – 10 hours or longer	Bupivacaine Ropivacaine Tetracaine Etidocaine Hexylcaine Cinchocaine

PHARMACOKINETICS OF LOCAL ANAESTHETICS:

Absorption:

Cutaneous absorption is poor except when they are applied on abraded areas. Mucosal absorption is good for all agents except procaine (topically ineffective). Tetracaine is better absorbed from mucosal sites, so useful as topical anaesthetic. Absorption after infiltration is faster with all agents. The rate of absorption will depend on the site of deposition of the drug.

Distribution:

Local anaesthetics are distributed widely in the CNS (3-4 fold), lungs and kidneys (10-15 fold). Heart and liver also accumulate the drug significantly. The agents cross barriers like placental barrier, so dosing should be done cautiously in pregnant animals.

Biotransformation:

The liver is the main site of inactivation of local anaesthetics by esterases, amidases and conjugation reactions. The safer local anaesthetics are esters whose plasma half-life is short; e.g. procaine is hydrolyzed by plasma esterases and undergoes hepatic degradation. Some local anaesthetics are amides and undergo the slower hepatic inactivation only.

Excretion:

Renal excretion is the main elimination route for local anaesthetics. The excretory products include unaltered drug as well as its metabolites.

POTENTIATION OF LOCAL ANAESTHETICS:

It can be achieved clinically by two methods:-

1. **By decreasing absorption from the site of injection:**

   Vasoconstriction in and immediately around the site of local anaesthetic administration prolongs the duration of anaesthesia by decreasing its absorption. It also minimizes the blood levels and reduces the risk of systemic toxicity. Adrenaline is added to local anaesthetic solutions at concentrations ranging from 1:1,00,000 to 1:50,000 for the purpose.

2. **By increasing the spread of local anaesthetic solution:**

   Hyaluronidase when added to local anaesthetic solutions increases the diffusion or spread of the local anaesthetic and enhances the area of anaesthetization. The inclusion of 150-300 units of hyaluronidase per 100 ml of anaesthetic achieved by s.c. injection. However, the duration of anaesthesia is reduced, which can be overcome by adding epinephrine to the anaesthetic.

LOCAL ANAESTHETIC AGENTS (Individual Drugs):

a. **Cocaine:** It was the first local anaesthetic alkaloid isolated from the leaves of *Erythroxylon coca* by Albert Nieman in the year 1860; and it is regarded as the "mother of all local anaesthetics". Now-a-days, it is of historical significance only. Its CNS toxicity limits its use and hence replaced by other agents.

b. **Lidocaine (Lignocaine or Xylocaine):** It is used as 1-2% solution for epidural and nerve block anaesthesia in large and small animals. It is also used i.v. @ 2 mg/kg b.wt. (every 15-30 minutes) to control cardiac arrhythmia in dog.

c. **Procaine:** It is used for infiltration (1% in small animals and 2% in large animals), conduction block (2.5 ml of a 2% solution in small animals and 5-10 ml of 4% solution in large animals) and epidural anaesthesia (2%).

d. **Tetracaine:** It is used for topical anaesthesia in the eye (0.5 % in small animals and 1% in large animals), nose & throat and for spinal anaesthesia when both sensory and motor blockade is desired.

e. **Benzocaine:** It has been used to varying degrees in dentistry to provide anaesthesia of the gums & buccal mucosa.

f. **Bupivacaine:** Long acting. Four times more potent than Lidocaine and has duration of action ranging from 3 to 8 hours.

CLINICAL APPLICATIONS OF LOCAL ANAESTHETIC AGENTS:

(i) Topical anaesthesia (Surface anaesthesia) : Eyes-4% xylocaine jelly, 0.5-1% tetracaine solution. These are used for catheterization in urethra and endotracheal incubation in the trachea.

(ii) Infiltration and field block : Local anaesthetics used are procaine (1% in small animals and 2% in large animals), lignocaine (2%).

(iii) Conduction/ Nerve block : Local anaesthetics used are procaine (2%), lignocaine (2%). And mepivacaine (2%). Mepivacaine is best suited in case of horse.

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NEUROMUSCULAR BLOCKING AGENTS

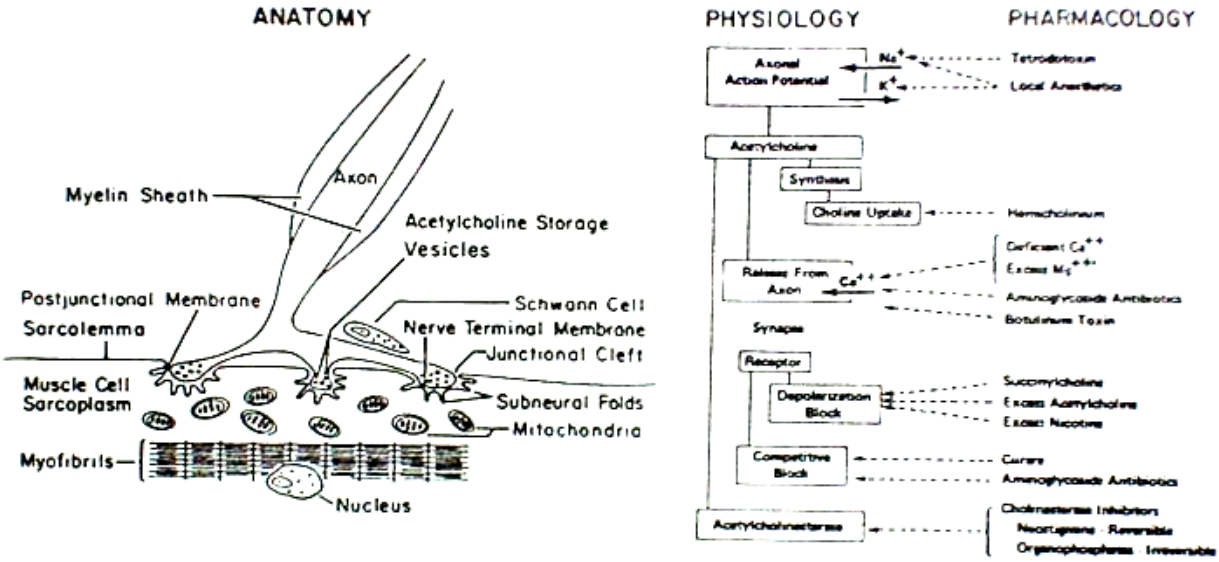

Fig.: Schematic representation of a somatic neuromuscular junction (synapse), related physiologic pathways, and proposed sites of action of various pharmacological agents. An axonal action potential (AP) is characterized by an influx of Na^+ and an efflux of K^+. Tetrodotoxin and saxitoxin inactivate Na^+ pathways. Local anaesthetics block Na^+ and K^+ pathways. Choline uptake into the neuron is blocked by hemicholinium; synthesis of ACh is prevented. As the AP arrives at the nerve terminal, it instigates inward movement of Ca^{++}; this triggers discharge of ACh into the junctional cleft. A lack of Ca^{++} or an excess of Mg^{++} decreases release of ACh. Aminoglycoside antibiotics also interfere with Ca^{++} - dependent release of ACh. Botulinum toxin inhibits ACh release. Decamethonium and succinylcholine (depolarizing neuromuscular blocking agents) cause persistent depolarization block of the motor end plate region, as do excess ACh and nicotine. Curare, gallamine and pancuronium (competitive neuromuscular blocking agents) compete with ACh for post-junctional receptors but do not cause depolarization. Aminoglycoside antibiotics decrease sensitivity of the post-junctional membrane to ACh. Catabolism of ACh by acetylcholinesterase is inhibited by reversible

Introduction:

Numerous drugs have been identified that inhibit transmission of nerve impulses at the somatic neuromuscular junction. Neuromuscular blocking agents used clinically act by interfering with the effectiveness of the endogenous neurotransmitter acetylcholine (ACh) to activate nicotinic cholinergic receptors of skeletal muscle cells. The end results of this action are skeletal muscle paralysis and muscular relaxation. Neuromuscular blocking agents are most often used as adjuvants to anaesthesia to facilitate tracheal intubation, abdominal muscle relaxation and orthopedic manipulations, and as part of balanced anaesthesia procedures to reduce the amount of general anaesthetic required.

History:

Development of neuromuscular blocking drugs originated with the discovery of **curare**, a tar like mixture of plant materials used as arrow poisons by South American tribes for game hunting. The animals got paralyzed even if not killed by the arrow. Natural sources of curare are *Chondodendron tomentosum* and *Strychnos toxifera*. Muscles paralyzing active principles of these are tubocurarine and toxiferine, respectively.

CENTRAL MUSCLE RELAXANTS:

The central muscle relaxants cause relaxation of skeletal muscles through central mechanisms, i.e. through CNS, unlike the peripheral neuromuscular blockers which act at the neuromuscular junctions. The central muscle relaxants cause specific CNS depression resulting in immobilization of the animals without affecting the consciousness.

(1) Mephenesin and Guaifenesin:

Mephenesin has very limited clinical value due to its potent adverse reactions such as venous thrombosis and haemolysis.

Guaifenesin is commonly used. It induces flaccid paralysis of skeletal muscles causing a selective inhibition of post-synaptic excitation of motor neurons of spinal cord. It is believed to act as a **glycine agonist**, the inhibitory transmitter in CNS, which mediates intraspinal post-synaptic inhibition. Strychnine and tetanus toxin by selective antagonism of glycine cause convulsions. Hence, strychnine and tetanus convulsions can be antagonized by guaifenesin.

Guaifenesin was first used for its analgesic, antipyretic and expectorant properties. It has been used as an adjunct to anaesthesia in horse. The compound increases the potency of preanaesthetic agents and barbiturates.

Guaifenesin is approved by the FDA as a muscle relaxant for use in the horse. It is used in horses as 5% solution in 5% dextrose saline as i.v. infusion as a preanaesthetic for casting. The effect of the drug is brief. Duration of action of a single muscle relaxant dose is 15 – 30 minutes.

(2) Diazepam:

Diazepam has anticonvulsant activity by facilitating or enhancing the action of central inhibitory transmitter GABA. GABA mediates inhibitory action of local interneurons in brain and pre-synaptic inhibition in spinal cord. Diazepam binds to a specific regulatory site on the GABA receptors and thereby enhancing neuronal inhibitory action of GABA. Diazepam effectively controls the convulsions induced by picrotoxin and leptazol, but not those of strychnine and tetanus. Diazepam is used in dog @ 0.5 to 1 mg/kg i.v. or i.m. It also causes sedation when used for muscle relaxation.

(3) Baclofen:

It acts like GABA by selectively stimulating the pre-synaptic $GABA_B$ receptors. Its muscle relaxant effect is due to inhibition of both monosynaptic and polysynaptic activation of motor neurons in spinal cord.

The traditional muscle relaxants cause relaxation of skeletal muscles either acting at peripheral sites (neuromuscular junctions) or through central mechanisms. However, a unique class of drugs like **dantrolene** cause muscle relaxation by mechanisms totally independent of the above. It acts directly on skeletal muscles. It interferes with the release of Ca^{++} from sarcoplasmic reticulum in skeletal muscle fibres.

PERIPHERAL NEUROMUSCULAR BLOCKERS:

These drugs interfere with the impulse transmission between motor nerve endings and the skeletal muscle fibres (neuromuscular junction). The effect of neuromuscular blockade results in paralysis or relaxation of skeletal muscles; hence these drugs are also known as **skeletal muscle relaxants**.

Neuromuscular blockers have been classified into the following according to their mechanism of action:

(1) Competitive neuromuscular blockers:
   (a) Natural alkaloids: d-tubocurarine (d-TC).
   (b) Synthetic compounds: Alcuronium, pancuronium, atracurium, gallamine etc.

(2) Depolarizing neuromuscular blockers: Decamethonium and succinylcholine.

[NB: An α-toxin present in the venoms of the krait (*Bungarus multicinctus*) and cobra (*Naja naja*) cause paralysis by irreversible blockade of neuromuscular transmission**]**

Mechanism of action of neuromuscular blockers:

The competitive blockers act by competitively antagonizing the action of acetylcholine for its receptor sites at the motor end plate (cholinergic nicotinic receptors). These blockers do not cause depolarization, hence also called as non-depolarizing neuromuscular blockers.

The depolarizing blockers cause <u>persistent depolarization</u> of the post-synaptic membrane at the neuromuscular junction and make it non-responsive to acetylcholine released from the motor nerve endings. These drugs are also called as non-competitive neuromuscular blockers.

Both the blockers are antagonistic to each other, if one is administered prior to the other.

Pharmacological Effects:

(i) <u>Skeletal muscles</u>: Paralysis.

The neuromuscular blockade by competitive blockers can be overcome by administering anticholinesterase (antiChE) agents, but not that caused by depolarizing blockers. The paralysis of muscles is preceded by transient muscular twitching or fasciculations with depolarizing neuromuscular blockers.

(ii) <u>Histamine release</u>: d-tubocurarine is a histamine liberator. The other neuromuscular blockers including both succinylcholine and decamethonium are weak histamine liberators.

(iii) <u>Cardiovascular system (CVS)</u>: Rapid i.v. injection of d-TC esp. at high doses, causes hypotension due to release of histamine. Gallamine slightly increases heart rate and cardiac output due to vagal blockade.

Therapeutic uses:

(i) As preanaesthetic before surgical anaesthesia to induce adequate skeletal muscle relaxation.
(ii) For the control or restraint of uncooperative animals (esp. ferocious wild animals).
(iii) For control of convulsions.
(iv) For the capture of wild animals.

Doses of neuromuscular blockers:

d-tubocurarine:	Dog & cat	0.4 to 0.5 mg/kg i.v.
	Pig	0.2 to 0.3 mg/kg i.v.
	Lamb & calf	0.05 to 0.06 mg/kg i.v.
Gallamine:	Dog & cat	1 mg/kg i.v.
	Lamb & calf	0.4 mg/kg i.v.
	Horse	0.5 to 1 mg/kg i.v.
Succinylcholine:	Dog	0.2 to 0.5 mg/kg i.v.
(Suxamethonium)	Cat	1 mg/kg i.v.
	Pig	2 mg/kg i.v.
	Cattle & sheep	0.01 to 0.02 mg/kg i.v.
	Horse	0.09 mg/kg i.v.

Muscle relaxant antagonists:

The competitive voluntary muscle relaxants can be antagonized by anticholinesterase (antiChE) drugs, esp. neostigmine following the administration of atropine, or the very short acting edrophonium chloride. Depolarizing agents can't be countered by these antagonists.

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