GENERAL ANAESTHETICS

DEFINITION:

- General anaesthetics are drugs which produce reversible loss of all sensation and consciousness.
- Anesthesia provides these five important benefits:
  - ✓ Sedation and reduction of anxiety
  - ✓ Lack of awareness and amnesia
  - ✓ Skeletal muscle relaxation
  - ✓ Suppression of undesirable reflexes
  - ✓ Analgesia

CRITERIA OF GA

- Be safe with minimal effects on the body system.
- Ensure rapid induction
- Facilitate early recovery from anaesthesia.
- Undergo minimal interaction with other agents.
- Undergo minimal metabolism in the body.
- Be easy to manufacture, store, and transport.

PROPERTIES OF AN IDEAL ANAESTHETIC:

- **FOR THE PATIENT**
  - ✓ It should be pleasant, non irritating, should not cause nausea or vomiting. Induction and recovery should be fast with no after effects.
- **FOR THE SURGEON**
  - ✓ It should provide adequate analgesia, immobility and muscle relaxation. It should be noninflammable and nonexplosive so that cautery may be used
- **FOR THE ANAESTHETIST**
  - ✓ Administration should be easy, controllable and versatile.
  - ✓ Margin of safety should be wide
  - ✓ Heart liver and other organs should be no affected
  - ✓ It should be potent so that low concentrations are needed and oxygenation of the patient does not suffer.
  - ✓ It should be cheap, stable and easily stored

THE EFFECTS OF ANAESTHETICS ON THE NERVOUS SYSTEM:

- At the cellular level, the effect of anaesthetics is mainly to inhibit synaptic transmission.
- Inhibition of synaptic transmission could be the result of
  - ✓ Reduction of transmitter release,
  - ✓ Inhibition of the action of the transmitter, or
  - ✓ Reduction of the excitability of the postsynaptic cell.
- Though all three effects have been described, most studies suggest that
  - ✓ Reduced transmitter release and reduced postsynaptic response are the main factors.
  - ✓ A reduction of acetylcholine release has been shown in studies on peripheral synapses, and reduced sensitivity to excitatory transmitters (through inhibition of ligand-gated ion channels) occurs at both peripheral and central synapses.
- The action of inhibitory synapses may be enhanced by anaesthetics.
- Enhancement of inhibitory synaptic action occurs particularly with barbiturates , though similar effects also occur with volatile anaesthetics.

- Much effort has gone into identifying a particular brain region on which anaesthetics act to produce their effect.
- The most sensitive region appears to be the thalamic sensory relay nuclei and the deep layer of the cortex to which these nuclei project.
- This constitutes the route taken by sensory impulses reaching the cortex, so inhibition can result in a lack of awareness of sensory input.
- As the anaesthetic concentration is increased, all brain functions are affected, including motor control and reflex activity, respiration and autonomic regulation.
- Therefore, it is not possible to identify a critical 'target site' in the brain responsible for all the phenomena of anaesthesia.

SITE AND MECHANISM OF ACTION:

- Although the general anaesthetics are capable of depressing all the functional elements of the CNS including the spinal cord.
- Their clinical effects vary, depending upon their ability to localize within CNS and interact with target sites.
- Inhibition of motor response to pain, such as that caused by surgical incision, is primarily mediated by the spinal cord.
- By inhibiting the spinal cord activity, the general anaesthetics decrease the transmission of noxious stimuli ascending from the spinal cord to the brain, and therby decrease supra-spinal arousal.
- They also modify the descending signals and cause immobilization.
- Above the spinal cord, general anaesthetics globally depress blood flow and glucose metabolism and selectively alter neuro-transmission in multiple supra-spinal regions, making those areas electrically silent.
- Their behavioural and physiological effects, including hypnosis and amnesia, are mediated by the brain.
- The reticular activating system, thalamus, pons, amygdale and hippocampus are involved in cognition, memory, learning, sleep, and attentiveness.
- Although there is no evidence for specific targets for general anaesthetics, it is postulated that they affect these areas.
- Recent finding show that ligand gated ion channels are the major targets of anaesthetics action.
- The $GABA_A$ receptor gated Cl^- channels is the most important of these.
- Many inhalational anaesthetics, barbiturates, benzodiazepines and propofol potentiate the action of inhibitory transmitter GABA to open Cl^- channels.
- Each of the above anaesthetics appears to interact with its own specific binding site on the $GABA_A$ receptor Cl^- channel complex, but none binds to the GABA binding site as such; though some inhaled anaesthetics and barbiturates can directly activate Cl^- channels.
- Action of glycine in the spinal cord and medulla is augmentated by barbiturates, propofol and many inhalational anaesthetics.
- This action may block responsiveness to painful stimuli resulting in immobility of the anaesthetics and barbiturates, in adittion, inhibit the neuronal cation channel gated by nicotinic cholinergic receptor which may mediate analgesia and amnesia.
- N_2O and ketamine selectively inhibit the excitatory NMDA type of glutamate receptor.

- This receptor gates mainly Ca^{2+} selective cation channels in the neurons, inhibition of which appears to be the primary mechanism of anaesthetic action of ketamine as well as N_2O.

Stages of Anaesthesia

- When a slowly acting anaesthetic, such as ether, is given on its own, certain well-defined stages are passed through as its concentration in the blood increases.

Stage I-Analgesia

- Starts from beginning of anaesthetic inhalation and lasts upto the loss of consciousness.
- The subject is conscious but drowsy and also in dreamy stage.
- Responses to painful stimuli are reduced.
- The degree of analgesia actually varies greatly with different agents; it is pronounced with ether and nitrous oxide, but not with halothane.
- Very minor surgery can be done.

Stage II-Excitement

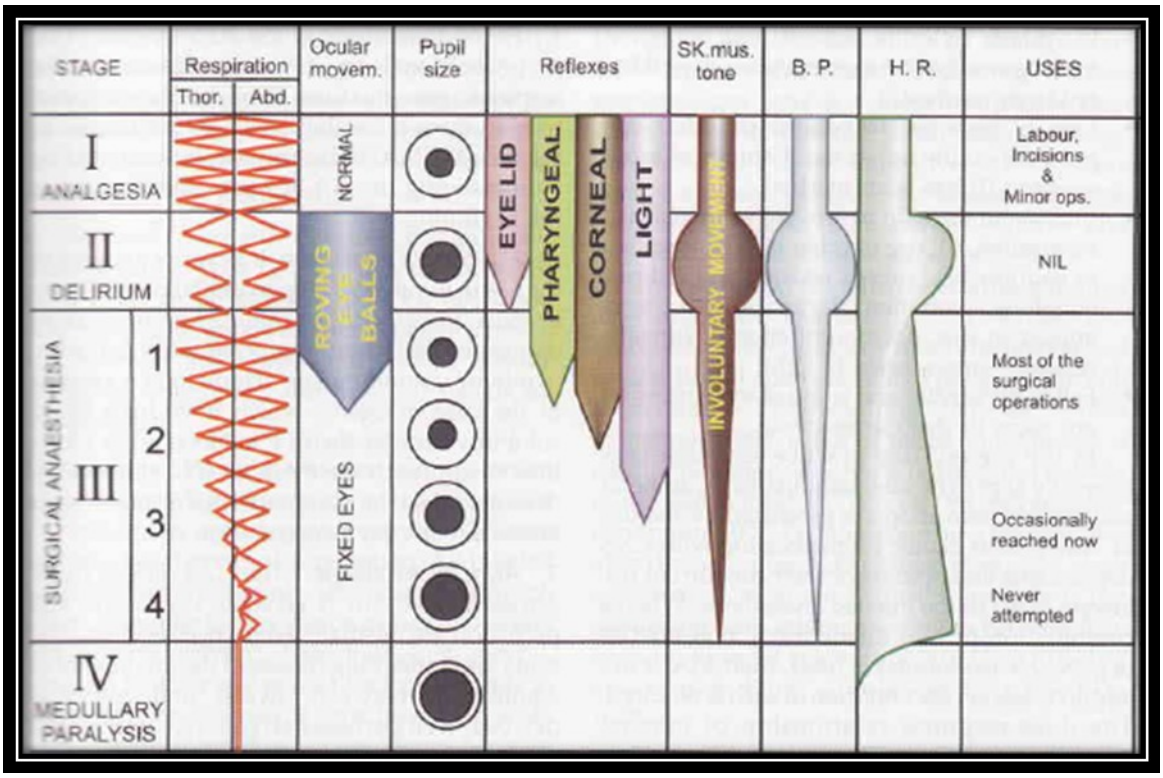
- The subject loses consciousness and no longer responds to non-painful stimuli but responds in a reflex fashion to painful stimuli.
- Other reflexes, for example the cough reflex and gagging in response to pharyngeal stimulation, are present and often exaggerated.
- The subject may move, talk incoherently, and hold his breath, choke or vomit.
- Heart rate and BP may rise and pupils dilate due to sympathetic stimulation
- Irregular ventilation may affect the absorption of the anaesthetic agent.
- It is a dangerous state, and modern anaesthetic procedures are designed to eliminate it.

Stage III-Surgical anaesthesia

- Spontaneous movement ceases and respiration becomes regular.
- If anaesthesia is light, some reflexes are still present, and muscles show appreciable tone.
- With deepening anaesthesia, these reflexes disappear, and the muscles relax fully.
- Respiration becomes progressively shallower, with the intercostal muscles failing before the diaphragm.
- This stage further divide in 4 stage
    1. Roving eyeballs. This plane ends when eyes become fixed.
    2. Loss of corneal and laryngeals reflexes.
    3. Pupil starts dilating and light reflex is lost
    4. Intercostal paralysis, shallow abdominal respiraton, dilated pupil
- BP falls, HR increase with weak pulse, respiration decreases in depth.

Stage IV-Medullary paralysis

- Respiration and vasomotor control cease, and death occur within a few minutes.
- Pupil is widely dilated, muscles are totally flabby, pulse is thready or imperceptible and BP is very low.
- Single anaesthetic agents are rarely used on their own, and progression through these stages is seldom observed in practice.



Techniques of Inhalationof Anaesthetics:

- **Open drop method**

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

Through Anaesthetic Machines

- **Open system**

  The exhaled gases are allowed to escap through a valve and fresh anaesthetic mixture is drawn in each time. No rebreathing is allowed-flow rates are high-more drug is consumed. However, inhaled O_2 and anaesthetic concentration can be accurately measured.

- **Closed system**

  The patient rebreaths the exhaled gas mixture after it has circulated through sodlime which absorbs CO_2 only as much O2 and anesthetic have been taken up by the patient are added to the circuit. The flow rates are low; specially useful for expensive and explosive agents. E.g. halothane, enflurane

- **Semiclosed system**

  Partial rebreathing is allowed through a partially closed valve. Conditions are intermediate with oderate flow rates**.**

Classification

- Inhalational
  - ✓ GAS
    - Nitrous oxide
  - ✓ LIQUIDS
    - Ether, Halothane, Enflurane, Isoflurane, Desflurane, Sevoflurane
- Intravenous
  - ✓ Inducing agents
    - Thipentone sod., Methohexitone sod, Propofol, Etomidate
  - ✓ Slower Acting Drugs
    - Benzodiazepines
      - Diazepam, Lorazepam, Midazolam
    - Dissociative anaesthesia
      - Ketamine
    - Opioid analgesic
      - Fentanyl

Inhalation Anaesthetics

- Inhaled gases are a mainstay of anesthesia and are used primarily for the maintenance of anesthesia after administration of an IV agent.
- No single anesthetic is superior to another under all circumstances.
- One advantage of inhalation anesthetics is that the depth of anesthesia can be rapidly altered by changing the inhaled concentration of the drug.
- Inhalational general anesthetics have very steep dose-response curves.
- In addition, they have a very narrow therapeutic index (generally from 2 to 4), so the difference in drug concentrations causing no effect, surgical anesthesia, and severe cardiac and respiratory depression is small.
- No antagonists exist.
- To minimize waste and decrease cost, potent inhaled anesthetic agents are delivered in a recirculation system containing absorbents that remove carbon dioxide and allow re-breathing of the inhaled anesthetic.

A. Common features of inhalation anesthetics

- Modern inhalation anesthetics are nonflammable, nonexplosive agents that include the gas *nitrous oxide* as well as a number of volatile, halogenated hydrocarbons.
- As a group, these agents decrease cerebrovascular resistance, resulting in increased perfusion of the brain.
- They also cause bronchodilation and decrease both spontaneous minute ventilation (volume of air per unit time moved into or out of the lungs) and hypoxic pulmonary vasoconstriction (increased pulmonary vascular resistance in poorly aerated regions of the lungs, which allows redirection of pulmonary blood flow to regions that are richer in oxygen content).
- The movement of these agents from the lungs to the different body compartments depends upon their solubility in blood and tissues as well as on blood flow.
- These factors play a role not only in induction, but also in recovery.

B. Potency

- The potency of inhaled anesthetics is defined quantitatively as the minimum alveolar concentration (MAC).

- This is the end-tidal concentration of anesthetic gas needed to eliminate movement among 50 percent of patients challenged by a standardized skin incision.
- **MAC is the median effective dose (ED_{50}) of the anesthetic.**
- MAC is usually expressed as the percentage of gas in a mixture required to achieve the effect.
- Numerically, MAC is small for potent anesthetics, such as sevoflurane, and large for less potent agents, such as *nitrous oxide* (N_2O).
- Therefore, the inverse of MAC is an index of the potency of the anesthetic.
- MAC values are useful in comparing pharmacologic effects of different anesthetics, because a high MAC equals low potency.
- Note that *nitrous oxide* alone cannot produce complete anesthesia, because an admixture with sufficient oxygen cannot approach its MAC value.
- The more lipid soluble an anesthetic, the lower the concentration of anesthetic needed to produce anesthesia and, thus, the higher the potency of the anesthetic.
- Factors that can increase MAC (and make the patient less sensitive) include hyperthermia (greater than 42° C), drugs that increase CNS catecholamines, and chronic *ethanol* abuse.
- Factors that can decrease MAC (and make the patient more sensitive) include increased age, hypothermia, pregnancy, sepsis, acute *ethanol* intoxication, concurrent administration of IV anesthetics, and α_2-adrenergic receptor agonists (such as *clonidine* and *dexmedetomidine*).

C. Uptake and distribution of inhalation anesthetics

- The principal objective of inhalation anesthesia is to achieve a constant and optimal brain partial pressure (Pbr) of the inhaled anesthetic (partial pressure equilibrium between alveoli [PA] and brain [Pbr]).
- Thus, the alveoli are the "windows to the brain" for inhaled anesthetics.
- The partial pressure of an anesthetic gas at the origin of the respiratory pathway is the driving force that moves the anesthetic into the alveolar space and, thence, into the blood, which delivers the drug to the brain and various other body compartments.
- Because gases move from one compartment to another within the body according to partial pressure gradients, a steady state is achieved when the partial pressure in each of these compartments is equivalent to that in the inspired mixture.
- **Note: At equilibrium, alveolar partial pressure = arterial partial pressure = brain partial pressure, or PA = Pa = Pbr.**
- The time course for attaining this steady state is determined by the following factors:

1. **Alveolar wash-in:**
   - This term refers to the replacement of the normal lung gases with the inspired anesthetic mixture.
   - The time required for this process is directly proportional to the functional residual capacity of the lung (the volume of gas remaining in the lungs at the end of a normal expiration) and inversely proportional to the ventilator rate.
   - It is independent of the physical properties of the gas. As the partial pressure builds within the lung, anesthetic transfer from the lung begins.
2. **Anesthetic uptake:**
   - Anesthetic uptake is the product of gas solubility in the blood, cardiac output, and the anesthetic gradient between alveolar and blood partial pressure gradients.

a. Solubility in the blood:

- This is determined by a physical property of the anesthetic molecule called the blood/gas partition coefficient, which is the ratio of the concentration of an anesthetic in the blood phase to the concentration of the anesthetic in the gas phase when the anesthetic is in equilibrium between the two phases.
- For inhaled anesthetics, think of the blood as a pharmacologically inactive reservoir.
- Drugs with low versus high solubility in blood differ in their speed of induction of anesthesia.
- For example, when an anesthetic gas with low blood solubility, such as *nitrous oxide*, diffuses from the alveoli into the circulation, little of the anesthetic dissolves in the blood.
- Therefore, the equilibrium between the inhaled anesthetic and arterial blood occurs rapidly, and relatively few additional molecules of anesthetic are required to raise arterial anesthetic partial pressure, thereby rapidly achieving a steady state.
- Agents with low solubility in blood, thus, quickly saturate the blood.
- In contrast, an anesthetic gas with high blood solubility, such as *halothane*, dissolves more completely in the blood, and greater amounts of the anesthetic and longer periods of time are required to raise blood partial pressure.
- This results in increased times of induction and recovery and slower changes in the depth of anesthesia in response to alterations in the concentration of the inhaled drug.
- The solubility in blood is ranked in the following order: *halothane* > *isofl urane* > *sevofl urane* > *nitrous oxide* > *desfl urane*.

b. Cardiac output:

- Cardiac output (CO) affects removal of anesthetic to peripheral tissues, which are not the site of action.
- For inhaled anesthetics, higher CO removes anesthetic from the alveoli faster (because of increased blood flow through the lungs) and thus slows the rate of rise in the alveolar concentration of the gas.
- It will therefore take longer for the gas to reach equilibrium between the alveoli and the site of action in the brain.
- Thus, for inhaled anesthetics, higher CO = slower induction.
- Again, for inhaled anesthetics, think of the blood as a pharmacologically inactive reservoir.
- A low CO (shock) speeds the rate of rise of the alveolar concentration of the gas, since there is less uptake (removal to peripheral tissues) to oppose input.

c. Alveolar to venous partial pressure gradient of the anesthetic:

- This is the driving force of anesthetic delivery.
- For all practical purposes, the pulmonary end-capillary anesthetic partial pressure may be considered equal to the alveolar anesthetic partial pressure if the patient does not have severe lung diffusion disease.

- The arterial circulation distributes the anesthetic to various tissues, and the pressure gradient drives free anesthetic gas into tissues.
- As the venous circulation returns blood depleted of anesthetic to the lung, more gas moves into the blood from the lung according to the partial pressure difference.
- The greater is the difference in anesthetic concentration between alveolar (arterial) to venous blood, the higher the uptake and the slower the induction.
- Over time, the partial pressure in the venous blood closely approximates the partial pressure in the inspired mixture. That is, no further net anesthetic uptake from the lung occurs.

3. Effect of different tissue types on anesthetic uptake:

- The time required for a particular tissue to achieve a steady state with the partial pressure of an anesthetic gas in the inspired mixture is inversely proportional to the blood flow to that tissue (that is, faster flow results in a more rapidly achieved steady state).
- It is also directly proportional to the capacity of that tissue to store anesthetic (that is, a larger capacity results in a longer time required to achieve steady state).
- Capacity, in turn, is directly proportional to the tissue's volume and the tissue/blood solubility coefficient of the anesthetic molecules. Four major tissue compartments determine the time course of anesthetic uptake:

a. Brain, heart, liver, kidney, and endocrine glands:

- These highly perfused tissues rapidly attain a steady state with the partial pressure of anesthetic in the blood.

b. Skeletal muscles:

- These are poorly perfused during anesthesia.
- This, and the fact that they have a large volume, prolongs the time required to achieve steady state.

c. Fat:

- This tissue is also poorly perfused.
- However, potent volatile general anesthetics are very lipid soluble.
- Therefore, fat has a large capacity to store anesthetic.
- This combination of slow delivery to a high-capacity compartment prolongs the time required to achieve steady state in that tissue.

d. Bone, ligaments, and cartilage:

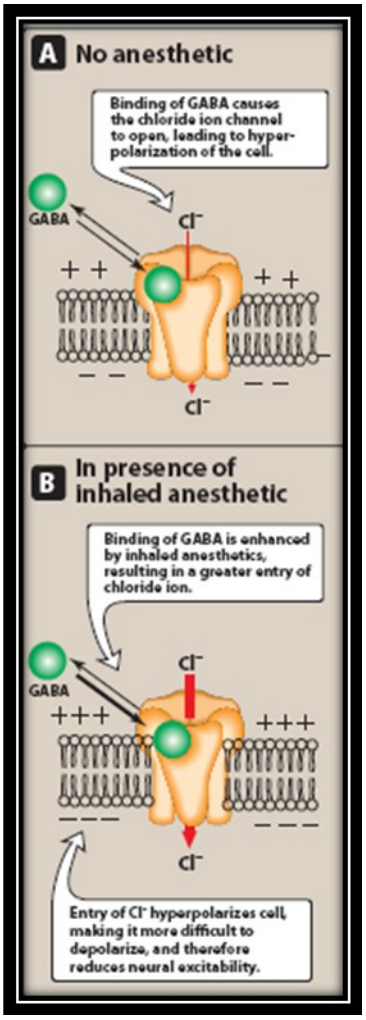
- These are poorly perfused and have a relatively low capacity to store anesthetic.
- Therefore, these tissues have only a slight impact on the time course of anesthetic distribution in the body.

4. Washout:

- When the administration of an inhalation anesthetic is discontinued, the body becomes the "source" that drives the anesthetic into the alveolar space.
- The same factors that influence attainment of steady state with an inspired anesthetic determine the time course of clearance of the drug from the body.
- Thus, *nitrous oxide* exits the body faster than *halothane.*

D. Mechanism of action

- No specific receptor has been identified as the locus of general anesthetic action.
- Indeed, the fact that chemically unrelated compounds produce the anesthetic state argues against the existence of such a receptor.
- The focus is now on interactions of the inhaled anesthetics with proteins comprising ion channels.
- For example, the general anesthetics increase the sensitivity of the γ-aminobutyric acid ($GABA_A$) receptors to the neurotransmitter, GABA, at clinically effective concentrations of the drug.
- This causes a prolongation of the inhibitory chloride ion current after a pulse of GABA release.
- Postsynaptic neuronal excitability is, thus, diminished.
- Other receptors are also affected by volatile anesthetics.
- For example, the activity of the inhibitory glycine receptors in the spinal motor neurons is increased.
- In addition, the inhalation anesthetics block the excitatory postsynaptic current of the nicotinic receptors.
- The mechanism by which the anesthetics perform these modulatory roles is not understood.



Nitrous oxide

- Colourless, odourless, heavier than air, noninflammable gas supplied under pressure in steel cylinders.
- It is rapid in action, because of its low blood:gas partition coefficient , and is also an effective analgesic agent in concentrations too low to cause unconsciousness.
- Nitrous oxide, if administered along with air, produces a stage of excitement and delirium and also produces amnesia. Hence the name "Laughing gas".
- It is used in this way to reduce pain during childbirth.
- The potency of nitrous oxide is low; even at a concentration of 80% in the inspired gas mixture.
- Nitrous oxide does not produce surgical anaesthesia.
- Poor muscle relaxant; neuromuscular blockers are required.
- Little effects on respiration, heart, BP.
- Nontoxic to liver, kidney, brain.
- Given for brief periods, nitrous oxide is devoid of any serious toxic effects, but prolonged exposure (over 6 hours) causes inactivation of methionine synthase, an enzyme required for DNA and protein synthesis, resulting in bone marrow depression, which may cause anaemia and leucopenia.
- This does not normally occur with brief exposure to nitrous oxide, but prolonged or repeated use needs to be avoided.
- It should also be avoided in patients with anaemia related to vitamin B_{12} deficiency.
- Prolonged exposure to very low concentrations of nitrous oxide, far below the level causing anaesthesia, may affect protein and DNA synthesis very markedly, and nitrous oxide has been suspected to be a cause of the increased frequency of abortion and fetal abnormality among operating theatre staff.

Halothane:

- Fluorinated volatile liquid, sweet and fruity odour, colorless, nonirritant and noninflammable.
- It Produces loss of consciousness in a conc. Of 2 to 3 percent in oxygen vapour and the anaesthesia can be maintaines by using 1 to 2 percent of halothane vapour with oxygen and nitrous oxide.
- A special apparatus is necessary to achieve a precise control of concentration.

Advantages:

- Non-inflammable and non-irritant to the respiratory tract; hence not unpleasant for induction. It has a fruity odour.
- Inhibits pharyngeal and laryngeal reflexes, making tracheal incubation easy. It does not cause laryngospasm, bronchospasm or coughing but in fact causes bronchodilatation.
- Potent anaesthetic with speedy induction and recovery.
- Postoperative vomiting infrequent.
- Can induce controlled hypotension and a bloodless field; to be used only by experts for this purpose.

Disadvantages:

- Special apparatus is necessary.
- Muscular relaxation inadequate for abdominal surgery, unless combined with a muscle relaxant.
- Poor analgesic.

- Depresses respiration.
- Can raise intracranial tension due to cerebral vasodilatation.
- Cause hypotension by direct depression of myocardium, and may cause cardiac arrhythmias. This is a major drawback.
- Postoperative recovery of mental function slow. Shivering during recovery is common.
- Hepatocellular microsomal enzyme induction can occur; rarely, it cause allergic hepatic necrosis due to the toxic metabolite trifluoroacetyl chloride.
- Can cause malignant hyperthermia in susceptible individuals.

Diethyl ether:

- Colourless, volatile liquid with pungent odour
- Anaesthetic ether contains 96-98 % diethyl ether.
- Ether vapour is irritating. Ether, when exposed to air, moisture or light may form ether peroxides or acetic aldehydes, which are irritant.
- A concentration of 10-15 % of ether in the inspired air is usually required for induction while a conc of 4 to 5 % ensure a satisfactory maintenance of anaesthesia in plane III; with a conc of more than 7 % respiratory failure may develop.

Advantages:

- Can be administered without complicated apparatus and air can be used as a diluents and source of oxygen.
- Can be used during an emergency without pre-anaesthetic medication.
- Has a wide margin of safety.
- Excellent analgesic.
- Curarimimetic and hence causes satisfactory muscle relaxation.
- Reflex stimulant of respiration and bronchodilator.
- Less likely to precipitate cardiac arrhythmias.
- Little Hepato-/nephro-toxicity.
- Can be used during delivery
- Economical

Disadvantages:

- Inflammable and explosive, and therefore potentially hazardous; cautery cannot be used.
- Induction is slow and may be stormy; and recovery slow.
- Irritant and may cause nausea/vomiting. Increase in salivary and bronchial secretion may cause cough/laryngeal spasm.
- Rarely may cause convulsion, especially in children
- Exhibits cross tolerance with ethyl alcohol.

Isoflurane

- This is a liquid related to enflurane with uptake and excretion more rapid than halothane.
- Its pharmacological properties are similar to those of halothane but it is less liable to cause sensitization of the heart to catecholamines.

Advantages:

- Physically stable and non-inflammable
- Rapid induction and recovery of anaesthesia.
- Bronchodilator.
- Good muscle relaxant
- Potent coronary vasodilator, does not affect renal blood flow.
- Less likely to sensitize the myocardium to adrenaline

- Hepatotoxicity

Disadvantages:

- Pungent and respiratory irritant
- Causes peripheral arterial vasodilatation and cause coronary steal
- It does not protect against local ischemia.

Desflurane

- Introduced recently, is chemically similar to isoflurane but its lower solubility in blood and fat means that induction and recovery are faster.
- It is not appreciably metabolised.
- Its potency is lower than that of the drugs described above.
- At the concentrations used for induction (about 10%), desflurane causes some respiratory tract irritation, which can lead to coughing and bronchospasm.

Sevoflurane

- Another recent introduction, resembles desflurane but is more potent and does not cause respiratory irritation.
- It is partially (about 3%) metabolised, and detectable levels of fluoride are produced, though this does not appear to be sufficient to cause toxicity.
- Like other halogenated anaesthetics, sevoflurane can cause malignant hyperthermia in genetically susceptible individuals.
- Many inhalation anaesthetics have been introduced and gradually superseded, mainly because of their inflammable nature or because of toxicity.

Intravenous Anaesthetic Agents:

- IV anesthetics cause the rapid induction of anesthesia.
- This is often described as occurring within one "arm-brain circulation time" or the time it takes the drug to travel from the site of injection (usually the arm) to the brain, where it has its effect.
- Anesthesia may then be maintained with an appropriate inhalation agent.
- IV anesthetics may be used as the sole agents for short procedures or administered as infusions to help maintain anesthesia during longer procedures. In lower doses, they may be used to provide sedation.

A. Induction

- After entering the blood stream, a percentage of the drug binds to the plasma proteins, and the rest remains unbound or "free."
- The degree of protein binding depends upon the physical characteristics of the particular drug, such as degree of ionization and lipid solubility.
- The drug is carried by venous blood to the right side of the heart, through the pulmonary circulation, and via the left side of the heart into the systemic circulation.
- The majority of the CO (70 percent) flows to the brain, liver, and kidney ("vessel-rich organs").
- Thus, a high proportion of the initial drug bolus is delivered to the cerebral circulation and then passes along a concentration gradient from the blood into the brain.
- The rate of this transfer is dependent on the arterial concentration of the unbound free drug, the lipid solubility of the drug, and the degree of ionization.
- Unbound, lipid-soluble, non-ionized molecules cross the blood-brain barrier most quickly.
- Once the drug has penetrated the CNS tissue, it exerts its effects.

- Like the inhalation anesthetics, the exact mode of action of the IV anesthetic drugs is unknown.

B. Recovery

- Recovery from IV anesthetics is due to redistribution from sites in the CNS.
- Following the initial flooding of the CNS and other vessel-rich tissues with non-ionized molecules, the drug starts to diffuse into other tissues with a lesser blood supply.
- With secondary tissue uptake, predominantly by skeletal muscle, the plasma concentration of the drug falls, allowing it to diffuse out of the CNS, down the resulting reverse concentration gradient.
- This initial redistribution of drug into other tissues leads to the rapid recovery seen after a single dose of an induction drug.
- Metabolism and plasma clearance become important only following infusions and repeat doses of a drug.
- Adipose tissue makes little contribution to the early redistribution of free drug following a bolus, due to its poor blood supply.
- However, following repeat doses or infusions, equilibration with fat tissue forms a drug reservoir, often leading to delayed recovery.

C. Effect of reduced cardiac output (CO)

- In circumstances in which CO is reduced the body compensates by diverting an increased proportion of the CO to the cerebral circulation to preserve cerebral blood flow.
- A greater proportion of any given drug will enter the cerebral circulation under these circumstances.
- As a result, the dose of induction drug must be reduced.
- Further, a decrease in CO leads to prolonged circulation time.
- That is, as global CO is reduced, the time taken for an induction drug to reach the brain and exert its effect is prolonged.
- The slow titration of a reduced dose of IV drug is key to a safe induction in patients with reduced CO.

Thiopental:

- Thiopental belongs to the barbiturate class of CNS depressants and is the only one of importance in anaesthesia.
- It has very high lipid solubility, and this accounts for the speed of its effect when it is injected intravenously.
- The free acid is insoluble in water, so thiopental is given as the sodium salt.
- This solution is strongly alkaline and is unstable, so the drug must be dissolved immediately before it is used.

Pharmacokinetic aspects

- On intravenous injection, thiopental causes unconsciousness within about 20 seconds, and this lasts for 5-10 minutes.
- The anaesthetic effect closely parallels the concentration of thiopental in the blood reaching the brain, because its high lipid solubility allows it to cross the blood-brain barrier without noticeable delay.
- The blood concentration of thiopental declines rapidly, by about 80% within 1-2 minutes, following the initial peak after intravenous injection, because the drug is redistributed,

first to tissues with a large blood flow (liver, kidneys, brain, etc.) and more slowly to muscle.

- Uptake into body fat, though favoured by the high lipid solubility of thiopental, occurs only slowly because of the low blood flow to this tissue.
- Recovery from the anaesthetic effect occurs within about 5 minutes, governed entirely by redistribution of the drug to well-perfused tissues; very little is metabolised in this time.
- After the initial rapid decline, the blood concentration drops more slowly, over several hours, as the drug is taken up by body fat and metabolised.
- Consequently, thiopental produces a long-lasting 'hangover'; furthermore, repeated intravenous doses cause progressively longer periods of anaesthesia, since the plateau in blood concentration becomes progressively more elevated as more drug accumulates in the body.
- For this reason, thiopental cannot be used to maintain surgical anaesthesia, but only as an induction agent.
- Thiopental binds to plasma albumin (roughly 70% of the blood content normally being bound).
- The fraction bound is less in states of malnutrition, liver disease or renal disease, which affect the concentration and drug-binding properties of plasma albumin; this can appreciably reduce the dose needed for induction of anaesthesia.

Actions and side-effects

- The actions of thiopental on the nervous system are very similar to those of inhalation anaesthetics, though it has no analgesic effect and can cause profound respiratory depression even in amounts that fail to abolish reflex responses to painful stimuli.
- Its long after-effect, associated with a slowly declining plasma concentration, means that drowsiness and some degree of respiratory depression persist for some hours.
- Accidental injection of thiopental around, rather than into, the vein or into an artery can cause local tissue necrosis and ulceration or severe arterial spasm, which can result in gangrene.
- Immediate injection of procaine, through the same needle, is the recommended procedure if this accident occurs.
- The risk is small, now that lower concentrations of thiopental are used for intravenous injection.

Etomidate:

- Etomidate 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 metabolised than thiopental and, therefore, less likely to cause a prolonged hangover.
- In other respects, etomidate is very similar to thiopental, though it appears more likely to cause involuntary movements during induction, and to cause postoperative nausea and vomiting.
- With prolonged use, etomidate appears to suppress the adrenal cortex, which has been associated with an increase in mortality in severely ill patients.
- It is, therefore, only used as an induction agent, and is preferable to thiopental in patients at risk of circulatory failure.

Propofol

- Propofol, introduced in 1983, is also similar in its properties to thiopental but has the advantage of being very rapidly metabolised and, therefore, giving rapid recovery without any hangover effect.
- This enables it to be used as a continuous infusion to maintain surgical anaesthesia without the need for any inhalation agent.
- Propofol lacks the tendency to cause involuntary movement and adrenocortical suppression seen with etomidate .
- It is particularly useful for the growing practice of day-case surgery.

Other Induction Agents Ketamine

- Ketamine closely resembles, both chemically and pharmacologically, **phencyclidine**,
- Both drugs produce a similar anaesthesia-like state and profound analgesia, but ketamine produces considerably less euphoria and sensory distortion than phencyclidine and is thus more useful in anaesthesia.
- Both drugs are believed to act by blocking activation of one type of excitatory amino acid receptor (the NMDA-receptor).
- Given intravenously, ketamine takes effect more slowly (2-5 minutes) than thiopental and produces a different effect, known as 'dissociative anaesthesia' in which there is a marked sensory loss and analgesia, as well as amnesia and paralysis of movement, without actual loss of consciousness.
- During induction and recovery, involuntary movements and peculiar sensory experiences often occur.
- Ketamine does not act simply as a depressant, and it produces cardiovascular and respiratory effects quite different from those of most anaesthetics.
- Blood pressure and heart rate are usually increased, and respiration is unaffected by effective anaesthetic doses.
- These after-effects limit the usefulness of ketamine but are said to be less marked in children;* therefore, ketamine, often in conjunction with a benzodiazepine, is often used for minor procedures in paediatrics.

Disadvantages

- It sometimes causes nystagmus, involuntary movements and hypertonus.
- It may cause delirium, hallucinations and colourful dreams during induction and recovery, especially in adults. Diazepam and midazolam given rapidly abolishes these disturbances.
- Rarely, laryngospasm may occur: salivation may be troublesome.
- Muscular relaxation is inadequate.
- It increases intraocular and intracranial pressures.
- It is a drug of abuse.

Not used in:

- In patients suffering from hypertension, cardiac decompensation or a cerebrovascular accident
- For surgery of the pharynx, larynx or bronchi.
- In abdominal surgery, as it relieves visceral pain poorly.
- In throtoxic patients, in whom it may cause rise in blood pressure.
- In pregnant women at term, because of its oxytocic activity. However, it may be used during caesarian section as it causes less fetal and neonatal depression.

- During operations on the eye, as it causes a rise in the intraocular pressure.
- In the presence of psychiatric disorders such as acute psychosis and schizophrenia.

Midazolam

- Midazolam, a benzodiazepine, is appreciably slower in the onset and offset of its action than the drugs discussed above, but it lacks the tendency to cause respiratory and cardiovascular depression, which can be an advantage in some patients.
- It is often used as a preoperative sedative for procedures such as endoscopy where full anaesthesia is not required.

Drug Interactions

- Patients on antihypertensives given general naesthetics- BP may fall markedly
- Neuroleptics, opioids, colnidine and monoamine oxidase inhibitors potentate anaesthetics
- Halothane, sensitizes heart to Adr.
- Insulin need of a diabetic is increased during GA: switch over to plan insulin even if he patient is on oral hypoglycaemics.

Preanaesthetic medication:

- Pre-anaesthetic medication is the term applied to the use of drugs prior to the administration of an anaesthetic agent, with the object of making anaesthesia safer and more agreeable to the patient.
- The reasons for such medication are:
  - ✓ For sedation, to reduce anxiety and apprehension without producing much drowsiness.
  - ✓ To obtain an additive or synergistic effect so that induction could be smooth and rapid and the dose of the general anaesthetic could be reduced.
  - ✓ To counteract certain adverse effects of the anaesthetic drug used such as salivation, bradycardia and vomiting.
  - ✓ To relieve pre- and post-operative pain.
  - ✓ To suppress respiratory secretions and to reduce reflex excitability.
- One or more drugs may be used in a patient depending on the needs.
- **Opioids:**

  Morhine or pethidine , i.m. anxiety and apprehension of the operation, produce pre- and post-operative analgesia, smoothen induction, reduce the dose of anaesthetics required and supplement poor analgesic.

  Disadvantages: they depress respiration interfere with pupillary signs of anaesthesia, may cause fall in BP during anaesthesia, can precipitate asthma and tend to delay recovery.

  Other are lack of amnesia, flushing, delayed gastric emptying and biliary spasm.

  Also contributes to postoperative constipation, vomiting and urinary retention.
- **Sedative-antianxiety drugs:**
  - ✓ Benzodiazepines like diazepam or lorazepam have become popular drugs for preanaesthetics medication because they produce tranquility and smoothen induction; there is loss of recall of perioperative events with little respiratory depression or accentuation of postoperative vomiting.
  - ✓ They counteract CNS toxicity of local anaesthetics and are being are used along with pethidine/fentanyl for a variety minor surgical and endoscopic procedure.

- ✓ Midazolam is a good amnesic with potent and shorter lasting action; it is also better suited for injection.

- **Anticholinergics:**
  - ✓ Atropine or hyoscine has been used, primarily to reduce salivery and bronchial secretions.
  - ✓ The main aim of their use now is prevent vagal bradycardia and hypotension, and prophylaxis of laryngospasm which is precipitated by respiratory secretions.
  - ✓ Hyoscine, in addition , produce amnesia and antiemetic effect, but tends to delay recovery.
  - ✓ Glycopyrrolate is a longer acting quarternary atropine substitute.it is potent antisecretory and antibradycardiac drug; acts rapidly and is less likely to produce central effects.
- **Neuroleptics**:
  - ✓ Chlorpromazine, triflupromazine or haloperidol i.m. are infrequently used in premedication.
  - ✓ They allay anxiety, smoothen induction and have antiemetics action.
  - ✓ They potentiate respiratory depression and hypotension caused by the anaesthetics and delay recovery.
  - ✓ Involuntary movements and muscle dystonias can occur, specially in children.
- **H_2 blockers:**
  - ✓ Patients undergoing prolonged operations, caesarian section, obese patients are at increased risk of gastric regurgitation and aspiration pneumonia.
  - ✓ Ranitidine or Famotidine given night before and in the morning benefit by raising pH of gastric juice; may also reduce its volume and thus chances of regurgitation.
  - ✓ Prevention of stress ulcers is another advantages.
- **Antiemetics:**
  - ✓ **Metoclopramide:**
    - Preoperatively is effective in reducing post operative vomiting.
    - By enhancing gastric emptying and tone of LES; it reduces the chances of reflux and its aspiration.
    - Extrapyramidal effects and motor restlessness can occur.
  - ✓ **Domperidone** is nearly as effective and does not produce extrapyramidal side effects.

Complications of General Anaesthesia

- During anasthesia
  - ✓ Respiratory depression
  - ✓ Salivation, respiratory secetions
  - ✓ Cardiac arrhythmisas
  - ✓ Fall in bp aspiration of gastric contents
  - ✓ Laryngospasm
  - ✓ Awareness
  - ✓ Delirium, convulsions
  - ✓ Fire and explosion
- After anaesthesia
  - ✓ Nausea and vomiting
  - ✓ Persisting sedation
  - ✓ Pneumonia

- ✓ Organ toxicities
- ✓ Nerve paralsies
- ✓ Emergence delirium
- ✓ Cognitive defects