GENERAL ANAESTHESIA

What is Anaesthesia

- **Anesthesia** – is a reversible condition of comfort, quiescence and physiological stability in a patient before, during and after performance of a procedure

- **General anesthesia** – for surgical procedure to render the patient unaware / unresponsive to the painful stimuli
  - Drugs producing G. Anaesthesia – are called General Anaesthetics

- **Local anesthesia** - reversible inhibition impulse generation and propagation in nerves. In sensory nerves, such an effect is desired when painful procedures must be performed, e.g., surgical or dental operations
  - Drugs producing Local Anaesthesia – are called Local Anaesthetics e.g. Procaine, Lidocaine and Bupivacaine etc.

General anaesthetics (Defn.)

- **General Anaesthetics** are the drugs which produce loss of all sensation and consciousness, or simply, a drug that affects the whole body and usually causes a loss of consciousness.

- **General anaesthetics** are – mainly ***inhalation or intravenous***

Ideal Properties of General Anesthetics

- **Loss of all sensations**
- **Sleep and Amnesia**
- **Immobility or Muscle relaxation**
- **Abolition of reflexes – somatic and autonomic**

Classification

- **Inhalation:**
  1. **Gas:** Nitrous Oxide
  2. **Volatile liquids:**
     - Ether
     - Halothane
     - Enflurane
     - Isoflurane
     - Desflurane
     - Sevoflurane

- **Intravenous:**
  1. **Inducing agents:**
     - Thiopentone, Methohexitone sodium, Propofol and Etomidate
  2. **Benzodiazepines (slower acting):**
     - Diazepam, Lorazepam, Midazolam
  3. **Dissociative anaesthesia:**
     - Ketamine
  4. **Opioid analgesia:**
     - Fentanyl

Mechanisms of GA

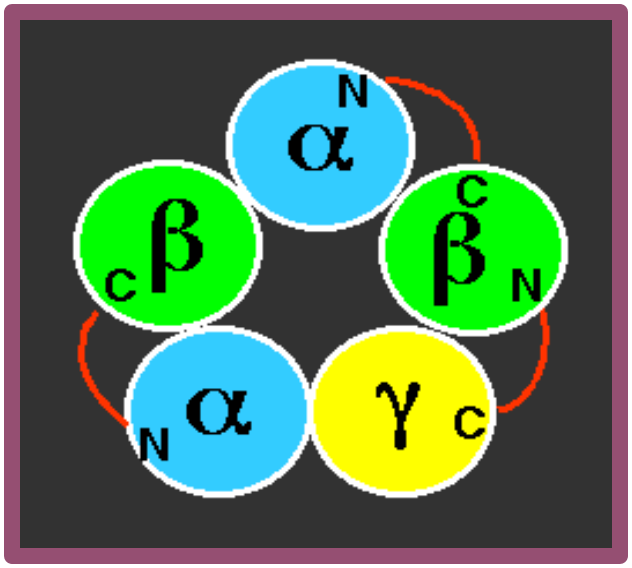
- Lipid : water partition coefficient
  - **GA (gases) are highly lipid soluble and therefore can easily enter in neurones**
  - After entry causes disturbances in physical chemistry of neuronal membranes – fluidization theory
  - Finally, abolition of Na+ channel and refusal of depolarization

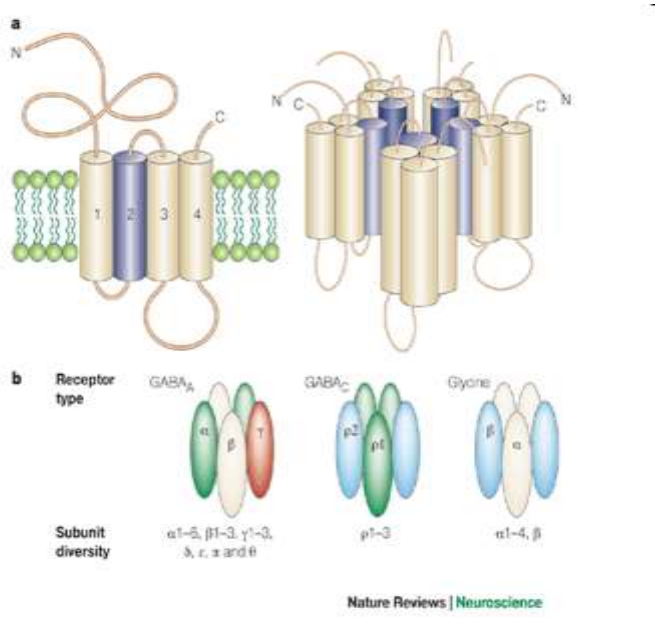
Modern theory on Mechanism of General Anesthesia

- **Major targets –** ligand gated ion channels
- **Important one –** $GABA_A$ receptor gated Cl^- channel
  - Examples – Many inhalation anesthetics, barbiturates, benzodiazepines and propofol
  - Potentiate the GABA to open the Cl^- channels

Structure of GABAA?

- $GABA_A$ receptors - 4 transmembrane (4-TM) ion channel
  - 5 subunits arranged around a central pore: 2 alpha, 2 beta, 1 gamma
  - Each subunit has N-terminal extracellular chain which contains the ligand-binding site
  - 4 hydrophobic sections cross the membrane 4 times: one extracellular and two intracellular loops connecting these regions, plus an extracellular C-terminal chain

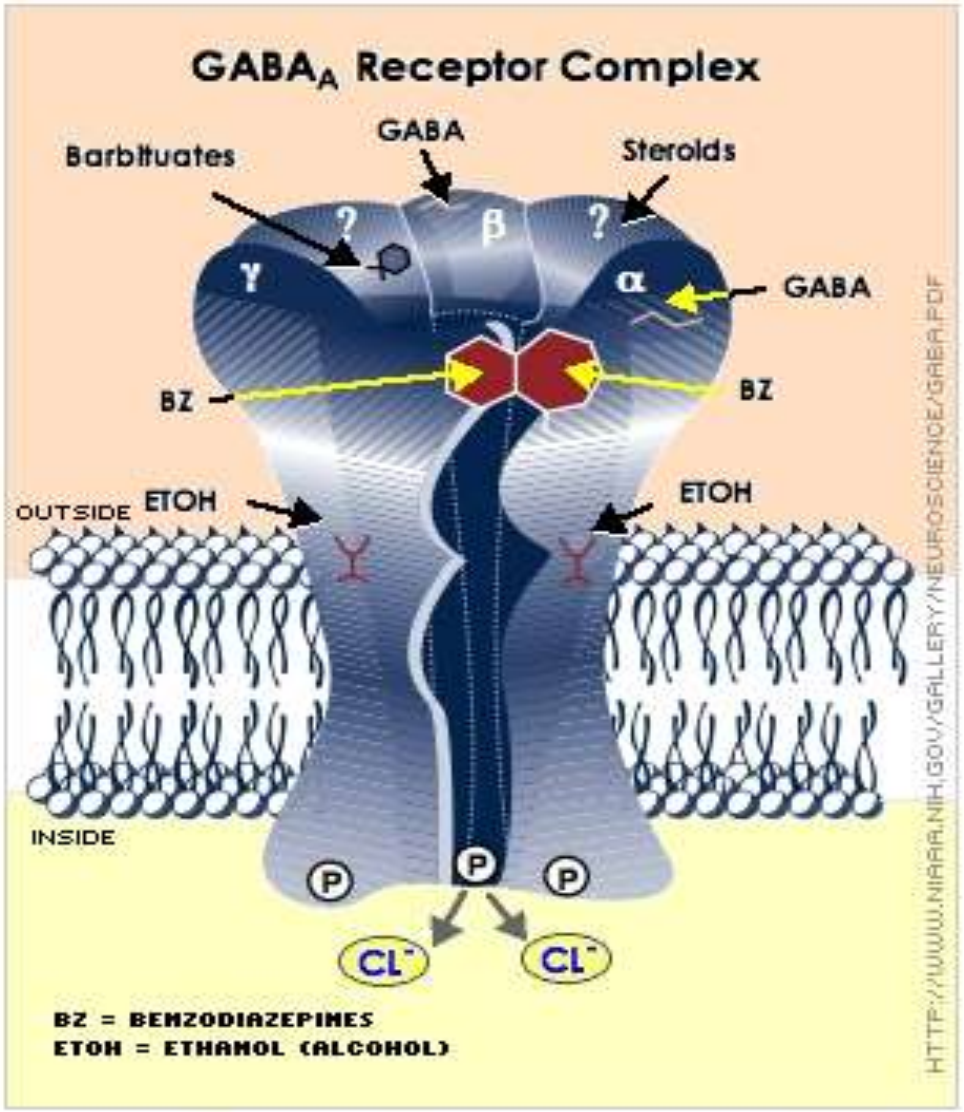




$GABA_A$ Receptor gated Cl^- Channel

- Normally, $GABA_A$ receptor mediates the effects of gamma-amino butyric acid (GABA), the major inhibitory neurotransmitter in the brain
  - $GABA_A$ receptor found throughout the CNS
    - most abundant, fast inhibitory, ligand-gated ion channel in the mammalian brain
    - located in the post-synaptic membrane
    - Ligand binding causes conformational changes leading to opening of central pore and passing down of Cl- along concentration gradient
    - Net inhibitory effect reducing activity of Neurones
  - General Anaesthetics bind with these channels and cause opening and potentiation of these inhibitory channels – leading to inhibition and anaesthesia

GABA Receptors – contd.



- Receptor sits on the membrane of its neuron at the synapse
- GABA, endogenous compound, causes GABA to open
- Drugs (GA) don't bind at the same side with GABA
- GA receptors are located between an alpha and beta subunit

Mechanism of GA – contd.

Other Mechanisms:

- Glycine – Barbiturates, propofol and others can activate in spinal cord and medulla
- N – methyl D- aspartate (NMDA) type of glutamate receptors - Nitrous oxide and ketamine selectively inhibit

STAGES OF GENERAL ANAESTHETICS
STAGE I

Stage I: Stage of Analgesia

- Starts from beginning of anaesthetic inhalation and lasts upto the loss of consciousness
- Pain is progressively abolished during this stage
- Patient remains conscious, can hear and see, and feels a dream like state
- Reflexes and respiration remain normal
- It is difficult to maintain - use is limited to short procedures only

stages of GA – contd.

Stage II: Stage of Delirium and Excitement:

- From loss of consciousness to beginning of regular respiration
- Excitement - patient may shout, struggle and hold his breath
- Muscle tone increases, jaws are tightly closed.
- Breathing is jerky; vomiting, involuntary micturition or defecation may occur.
- Heart rate and BP may rise and pupils dilate due to sympathetic stimulation.
- No stimulus or operative procedure carried out during this stage.
- Breatholding are commonly seen. Potentially dangerous responses can occur during this stage including vomiting, laryngospasm and uncontrolled movement.
- **This stage is not found with modern anaesthesia – preanaesthetic medication, rapid induction etc.**

stages of GA – contd.

- **Stage III: Stage of Surgical anaesthesia**
  - Extends from onset of regular respiration to cessation of spontaneous breathing. This has been divided into 4 planes:
  - Plane 1: Roving eye balls. This plane ends when eyes become fixed.
  - Plane 2: Loss of corneal and laryngeal reflexes.
  - Plane 3: Pupil starts dilating and light reflex is lost.
  - Plane 4: Intercostal paralysis, shallow abdominal respiration, dilated pupil.

stages of GA – contd.

Stage IV: Medullary / respiratory paralysis

- Cessation of breathing ⟶ failure of circulation ⟶ death
- Pupils: widely dilated
- Muscles are totally flabby
- Pulse is imperceptible
- BP is very low.

signs & stages of GA – contd.

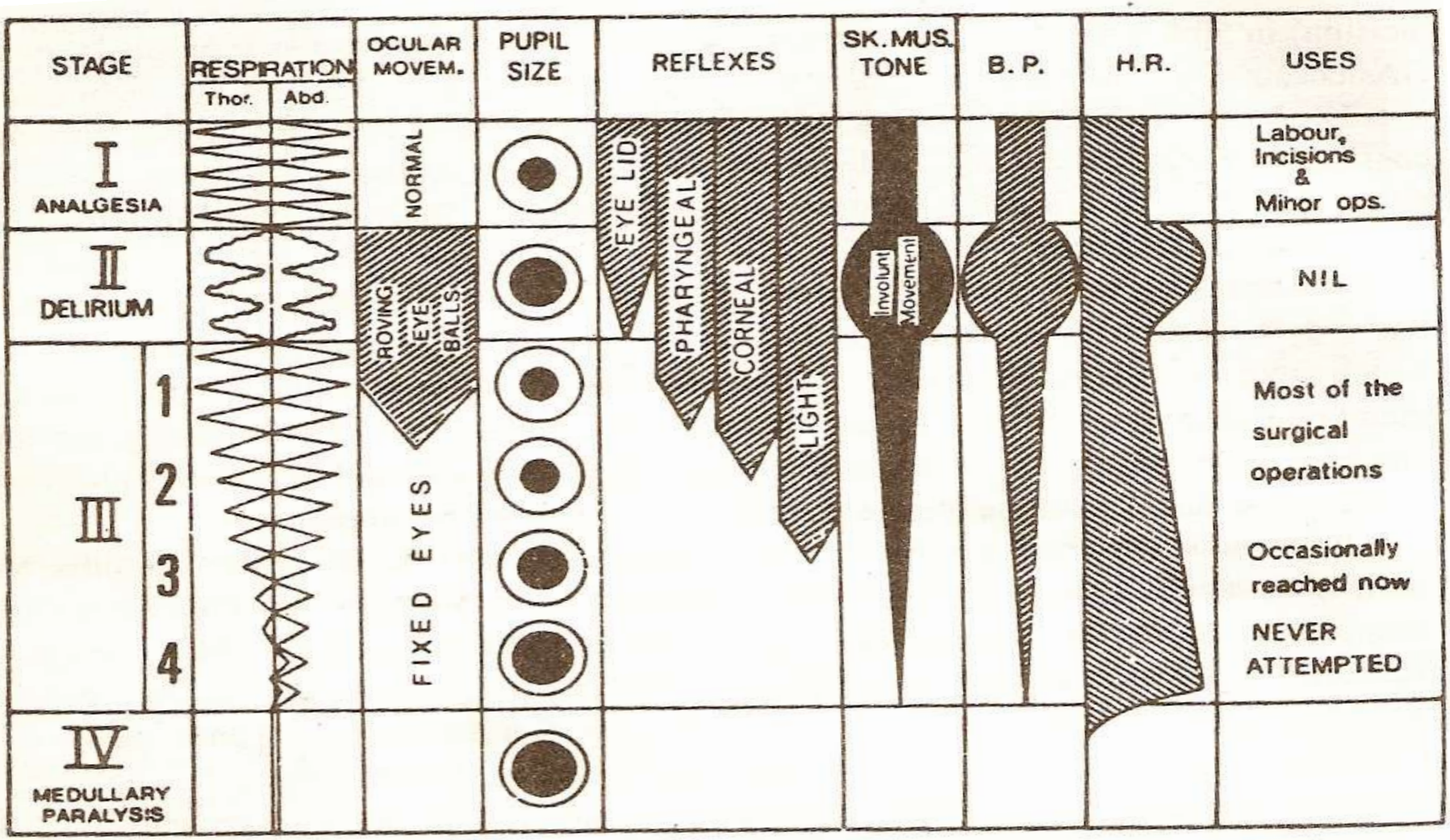


Fig. 23.1: Stages of

Properties of GA – contd.

- **For Patient:**
  - Pleasant, non-irritating and should not cause nausea or vomiting
  - Induction and recovery should be fast
- **For Surgeon:**
  - analgesia, immobility and muscle relaxation
  - nonexplosive and noninflammable
- **For the anaesthetist:**
  1. Margin of safety: No fall in BP
  2. Heart, liver and other organs: No affect
  3. Potent
  4. Cheap, stable and easily stored
  5. Should not react with rubber tubing or soda lime
  6. Rapid adjustment of depth of anaesthesia should be possible

1. Diethyl ether (C2H5 – O – C2H5)

- Colourless, highly volatile liquid with a pungent odour. Boiling point – 35ºC
- Produces irritating vapours and are inflammable and explosive
- Pharmacokinetics:
  - 85 to 90 percent is eliminated through lung and remainder through skin, urine, milk and sweat
  - Can cross the placental barrier

Ether – contd.

- Advantages
  - Can be used without complicated apparatus
  - Potent anaesthetic and good analgesic
  - Muscle relaxation
  - Wide safety of margin
  - Respiratory stimulation and bronchodilatation
  - Does not sensitize the heart to adrenaline
  - No cardiac arrythmias
  - Can be used in delivery
  - Less likely hepato or nephrotoxicity

- Disadvantages
  - Inflammable and explosive
  - Slow induction and unpleasant - atropine
  - Slow recovery – nausea & vomiting
  - Cardiac arrest
  - Convulsion in children
  - Cross tolerance – ethyl alcohol

2. Nitrous oxide/laughing gas (N_2O)

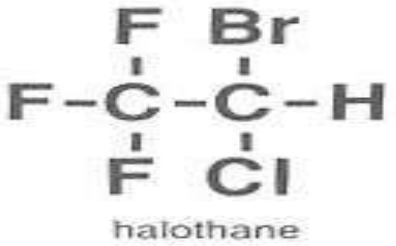
- NH_4NO_3 (s) → 2 H_2O (g) + N_2O (g)
- Colourless, odourless inorganic gas with sweet taste
- Noninflammable and nonirritating, but of low potency
- Very potent analgesic
- Carrier and adjuvant to other anaesthetics – 70% + 25-30% + 0.2-2%
- As a single agent used wit O_2 in dental extraction and in obstetrics

Nitrous oxide – contd.

- Advantages:
  - Non-inflammable and nonirritant
  - Rapid induction and recovery
  - Very potent analgesic (low concentration)
  - No nausea and vomiting
  - Nontoxic to liver, kidney and brain

- Disadvantages:
  - Not potent alone (supplementation)
  - Hypoxia
  - Inhibits methionine synthetase (precursor to DNA synthesis)
  - Inhibits vitamin B-12 metabolism
  - Dentists, OR personnel, abusers at risk
  - Gas filled spaces - dangerous

3. Halothane



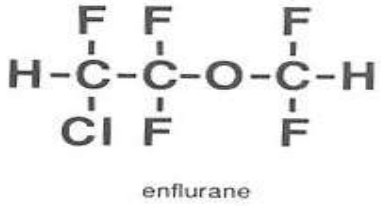
- Fluorinated volatile liquid with sweet odour, non-irritant non-inflammable and supplied in amber coloured bottle
- Potent anaesthetic, 2-4% for induction and 0.5-1% for maintenance
- Boiling point - 50ºC
- Pharmacokinetics: 60 to 80% eliminated unchanged. 20% retained in body for 24 hours and metabolized

Halothane – contd.

- Advantages:
  - Non-inflammable and non-irritant
  - Pharyngeal and laryngeal reflexes – bronchodilatation
  - Potent and speedy induction & recovery
  - Controlled hypotension
  - Inhibits intestinal and uterine contractions

- Disadvantages:
  - Special apparatus
  - Poor analgesic and muscle relaxation
  - Hypotension and – direct action (Ca++) and failure of sympathetic activity
  - Arrythmia
    - Direct vagal stimulation, direct depression of SA node and lack of baroreceptor action
  - Respiratory depression
  - Decreased urine formation – due to decreased gfr
  - Hepatitis: 1 in 10,000
  - Malignant hyperthermia: Ryanodine receptor
  - Prolong labour

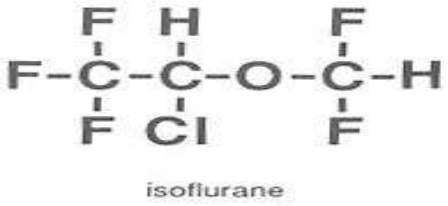
4. Enflurane:



enflurane

- Non-inflammable, with mild sweet odour and boils at 57ºC
- Similar to halothane in action, except better muscular relaxation
- Depresses myocardial force of contraction and sensitize heart to adrenaline
- Induces seizure in deep anaesthesia and therefore not used now - Epileptiform EEG
- Metabolism one-tenth that of halothane-- does not release quantity of hepatotoxic metabolites
- Metabolism releases fluoride ion-- renal toxicity

5. Isoflurane:



isoflurane

- Isomer of enflurane and have simmilar properties but slightly more potent
- Induction dose is 1.5 – 3% and maintenance dose is 1 – 2%
- By special vapourizer

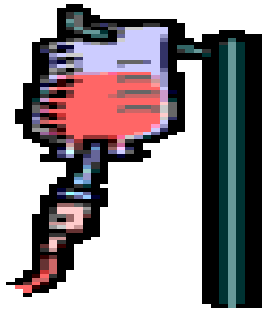
Isoflurane – contd.

- Advantages:
  - Rapid induction and recovery
  - Good muscle relaxation
  - Good coronary vasodilatation
  - Less Myocardial depression than no myocardial sensitization to adrenaline
  - No renal or hepatotoxicity
  - Low nausea and vomiting
  - No dilatation of pupil and no loss of light reflex in deep anaesthesia
  - No seizure and preferred in neurosurgery
  - Uterine muscle relaxation

- Disadvantages:
  - Pungent and respiratory irritant
  - Special apparatus required
  - Respiratory depression
  - Maintenance only, no induction
  - ß adrenergic receptor stimulation
  - Costly

Intravenous Anaesthetics:

- For induction only
- Rapid induction (one arm-brain circulation time
- For maintenance not used
- Alone – supplemented with analgesic and muscle relaxants



Intravenous:

- Inducing agents:

  Thiopentone, Methohexitone sodium, propofol and etomidate

  - Benzodiazepines (slower acting):

    Diazepam, Lorazepam, Midazolam

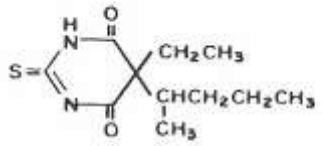
- Dissociative anaesthesia:

  Ketamine

- Neurolept analgesia:

  Fentanyl

Thiopentone sodium:

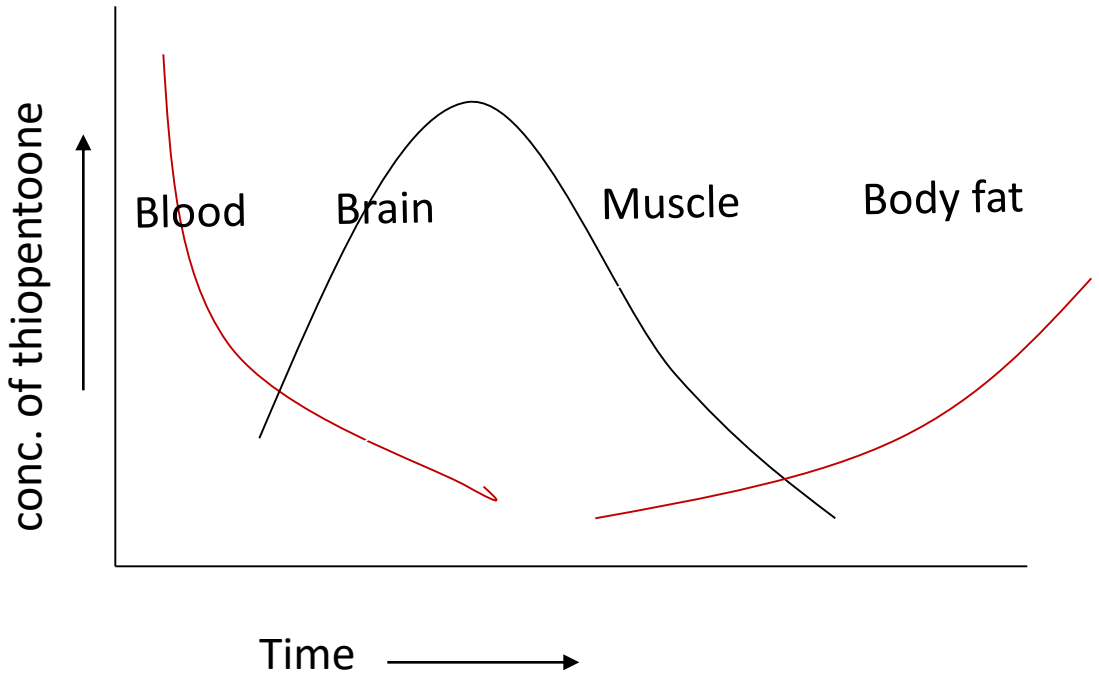


Thiopental

- Barbiturate: Ultra short acting
  - Water soluble
  - Alkaline
  - Dose-dependent suppression of CNS activity
  - Dose: 3-5mg/kg iv (2.5%) solution – 15 to 20 seconds
- Pharmacokinetics:
  - Redistribution
  - Hepatic metabolism (elimination half-life 7-12 hrs)
- CNS depression persists for long (>12 hr)

Tiopentone – contd,.

Redistribution:



Side effects of Thiopentone:

- Pre-anaesthetic course - laryngospasm
- Noncompatibility - succinylcholine
- Tissue necrosis--gangrene
- Post-anaesthetic course - analgesic

Thiopentone – contd.

- Advantages:
  - Rapid induction
  - Does not sensitize myocardium to adrenaline
  - No nausea and vomiting
  - Non-explosive and non-irritant\
  - Short operations (alone)
  - Other uses: convulsion, psychiatric patients and narcoanalysis of criminals

- Disadvantages:
  - Depth of anaesthesia difficult to judge
  - Pharyngeal and laryngeal reflexes persists - apnoea – controlled ventilation
  - Respiratory depression
  - Hypotension (rapid) – shock and hypovolemia
  - Poor analgesic and muscle relaxant
  - Gangrene and necrosis
  - Shivering and delirium

Thiopentone – contd.

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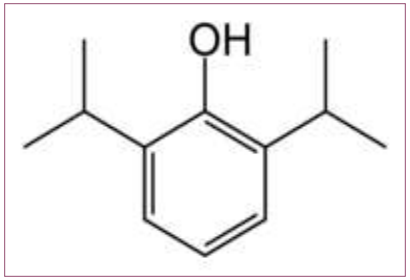
2. Propofol



- Replacing thiopentone now
- Oily liquid used as 1% emulsion
- Rapid induction (one arm-brain circulation time): 15 – 45 seconds and lasts for 5–10 minutes
- Rapid distribution – distribution half-life (2-4 min)
- Short elimination half-life (100 min)
- Dose: Induction - 2mg/kg bolus i.v.

  Maintenance - 9 mg/kg/hr i.v.
- Propofol is extensively metabolized
  - 88% of an administered dose appears in the urine
- Metabolized by hepatic conjugation of the inactive glucuronide metabolites

Propofol – contd.

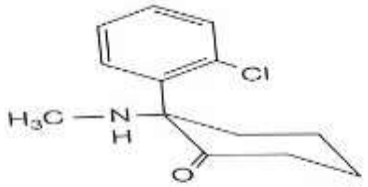
Advantages:

- Rapid induction
- Does not sensitize myocardium to adrenaline
- No nausea and vomiting
- Non-explosive and non-irritant
- Total i.v. anaesthesia
- Short operations (alone)

Disadvantages:

- Induction apnoea
- Hypotension
- Braddycardia
- Dose dependent respiratory depression
- Pain during injection: local anaesthetic combination

3. Ketamine:



Ketamine

- Phencyclidine derivative
- Dissociative anaesthesia: a state characterized by immobility, amnesia and analgesia with light sleep and feeling of dissociation from ones own body and mind and the surroundings.
- Site of action – cortex and subcortical areas – NMDA receptors
- Dose: 5-10mg/kg im or 1-2mg i.v.

Ketamine – contd.

- Disadvantages:
  - Limb movements and nystagmus
  - Emergence phenomenon – 50% patients
  - Hypertensives
  - Increase in IOT and ICP
  - Uterine stimulation
  - Psychosis and shizophrenia
  - Rare laryngospasm
  - Poor muscle relaxation

Ketamine – contd.

Uses:

1. Characteristics of sympathetic nervous system stimulation (increase HR, BP & CO) – hypovolumic shock
2. In head and neck surgery
3. In asthmatics
4. Short surgical procedures – burn dressing, forceps delivery, breech extraction manual removal of placenta and dentistry
5. Combination with diazepam - angiography, cardiac catheterization
6. OPD surgical procedures

4. Fentanyl

- Neurolept analgesia: droperidol
- 4-acylanilino derivative
- Opioid analgesic
- Duration of action: 30-50 min.
- Uses:

- in combination with diazepam used in diagnostic, endoscopic and angiographic procedures
- Adjunct to spinal and nerve block anaesthesia

Fentanyl – contd.

Advantages:

- Smooth onset and rapid recovery
- Suppression of vomiting and coughing
- Commanded operation
- Less fall in BP and no sensitization to adrenaline

Disadvantages:

- Respiratory depression
- Increase tone of chest muscle
- Nausea, vomiting and itching during recovery

Complications of anaesthesia:

During anaesthesia:

- Respiratory depression
- Salivation, respiratory secretions
- Cardiac arrhythmias
- Fall in BP
- Aspiration
- Laryngospasm and asphyxia
- Awareness
- Delirium and convulsion
- Fire and explosion

After anaesthesia:

- Nausea and vomiting
- Persisting sedation
- Pneumonia
- Organ damage – liver, kidney
- Nerve palsies
- Emergence delirium
- Cognitive defects

Preanesthetic medication:

- Definition:

  It is the term applied to the use of drugs prior to the administration of an anaesthetic agent to make anaesthesia safer and more agreeable to the patient.

- Aim:

  - Relief of anxiety
  - Amnesia for pre and post operative events
  - Analgesia
  - Decrease secretions
  - Antiemetic effects
  - Decrease acidity and volume of gastric juice

Preanaesthetic medication – contd.

- Drugs used:
  - ❖ Sedative-anxiolytics – diazepam or lorazepam, midazolam, promethazine etc.
  - ❖ Opioids – Morphine and its congeners
  - ❖ Anticholinergics – Atropine
  - ❖ H_2 blockers – ranitidine, famotidine etc.
  - ❖ Antiemetics – Metoclopramide, domperidone etc.