General Anaesthetics Pharmacology

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Content of the Lectures

- Introduction
- History
- Classification
- Ideal Properties
- Mechanism of Action
- Stages

General Anaesthetics (GAs)

- General anesthetics (GAs) are drugs which produce reversible loss of all sensation and consciousness.
- The cardinal features of general anaesthesia are:
  - Loss of all sensation, especially pain
  - Sleep (unconsciousness) and amnesia
  - Immobility and muscle relaxation
  - Abolition of somatic and autonomic reflexes.
- For achieving all features, we can use combination of Inhaled and i.v. Gas with preanesthetic agents

General Anaesthetics (GAs)

History:

- Before the middle of 19th century a number of agents like alcohol, opium, cannabis, or even concussion and asphyxia were used to obtund surgical pain, but operations were horrible ordeals
- **Horace Wells**, a dentist, picked up the idea of using **nitrous oxide** (N2O) from a demonstration of laughing gas in 1844.
- **Morton**, a dentist and medical student at Boston, after experimenting on animals, gave a demonstration of **ether** anaesthesia in 1846, and it soon became very popular
- Chloroform was used by Simpson in Britain for obstetrical purpose in 1847
- Cyclopropane was introduced in 1929, but the new generation of anaesthetics was heralded by halothane in 1956.
- The first i.v. anaesthetic thiopentone was introduced in 1935

Classification of General Anaesthetics (GAs)

1. Inhalational

- **A. Gas:** Nitrous oxide
- **B. Voletile Liquid:** Ether, Halothane, Isoflurane, Desflurane, Sevoflurane

2. Intravenous

- **A. Fast Acting:** Thiopentone sod., Methohexitone sod., Propofol, Etomidate
- **B. Slow Acting:**
  - **Benzodiazepines** (Diazepam, Lorazepam, Midazolam)
  - **Dissociative anaesthesia** (Ketamine)
  - **Opioid analgesia** (Fentanyl)

Properties of Ideal General Anaesthetics (GAs)

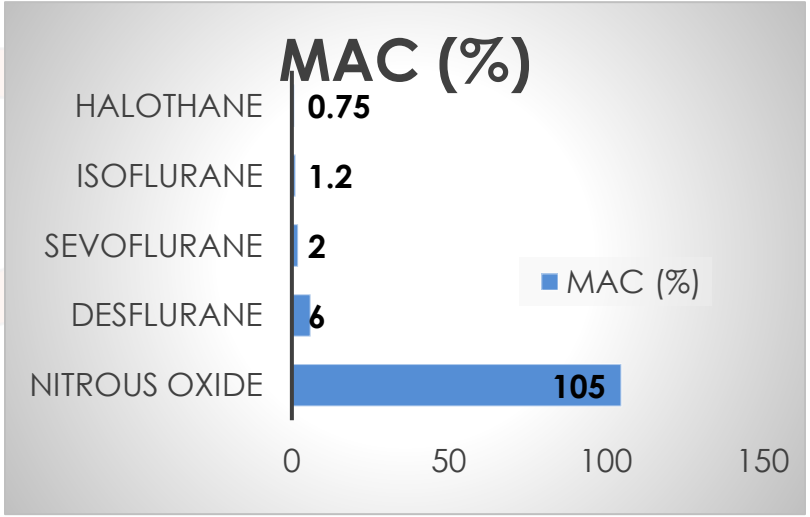
- **A. For the patient:** It should be pleasant, nonirritating, should not cause nausea or vomiting. Induction and recovery should be fast with no after effects
- **B. For the surgeon:** It should provide adequate analgesia, immobility and muscle relaxation. It should be noninflammable and nonexplosive so that cautery may be used.
- **C. For the anaesthetist**: Its administration should be easy, controllable and versatile.
  - Margin of safety should be wide—no fall in BP
  - Heart, liver and other organs should not be affected.
  - It should be potent so that low concentrations are needed and oxygenation of the patient does not suffer.
  - Rapid adjustments in depth of anaesthesia should be possible.
  - It should be cheap, stable and easily stored.
  - It should not react with rubber tubing or soda lime

Mechanism of Action of GAs

- The mechanism of action of GAs is not precisely known. So all GAs action had been related to some common physicochemical property of the drugs
- **Mayer and Overton (1901)** pointed out a direct parallelism between **lipid/water partition coefficient (Lipid solubility)** of the GAs and their anaesthetic potency. He proposed Minimal alveolar concentration (MAC).
- **Minimal alveolar concentration (MAC)** 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.
- MAC is the ED50 of the GA

Mechanism of Action of GAs

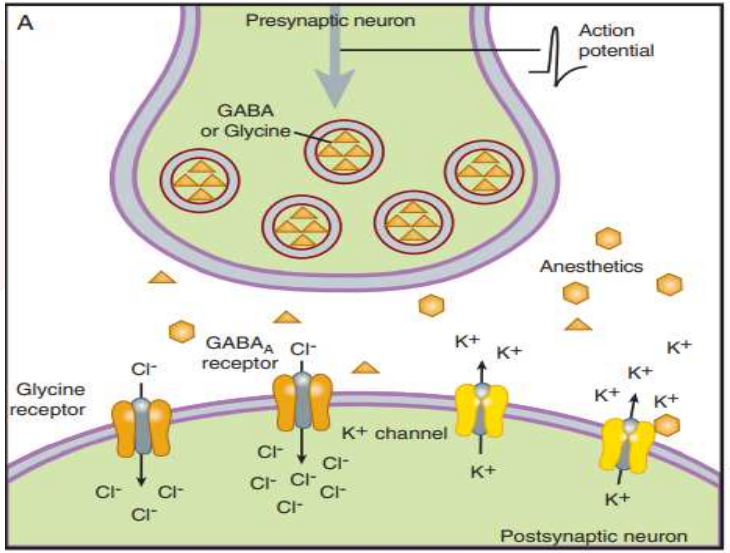
- **MAC** is accepted as a valid measure of potency of inhalational GAs, because it remains fairly constant for most young adults. The MAC of all inhalational anaesthetics declines progressively as age advances beyond 50 years.
- The MAC expressed as the % of gas in a mixture required to achieve the effects.
- **Conceptually Potency of GA inversely proportional to the MAC**



Mechanism of Action of GAs

Possible Pathways

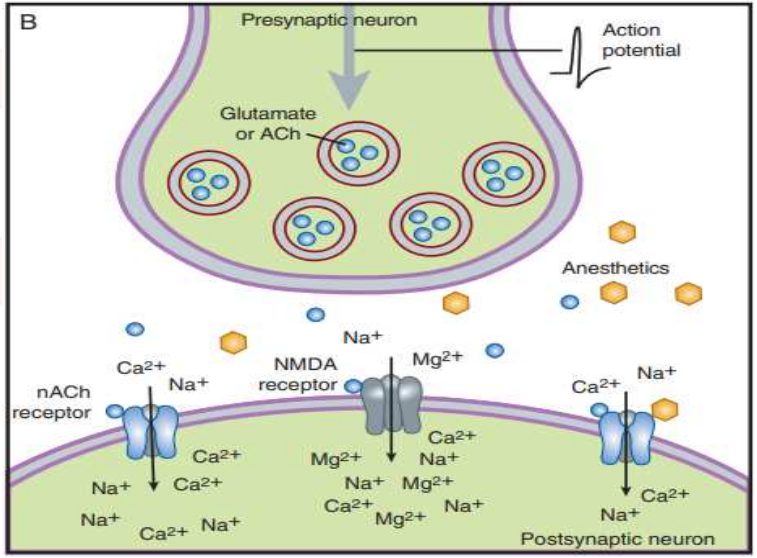
- **$GABA_A$ Mediated inhibitory Action** (Barbiturates, Benzodiazepenes, propofol, and some inhaled GA)
- **Glycine receptor mediated inhibitory action** in the spinal cord and medulla is augmented by barbiturates, propofol and many inhalational anaesthetics



Mechanism of Action of GAs

Possible Pathways

- Certain fluorinated anaesthetics and barbiturates, in addition, inhibit the neuronal cation channel gated by nicotinic cholinergic receptor which may mediate analgesia and amnesia.
- N2O and ketamine selectively inhibit the excitatory NMDA type of glutamate receptor.



Stages of Anaesthesia

Guedel (1920) described four stages with ether anaesthesia, dividing the III stage into 4 planes

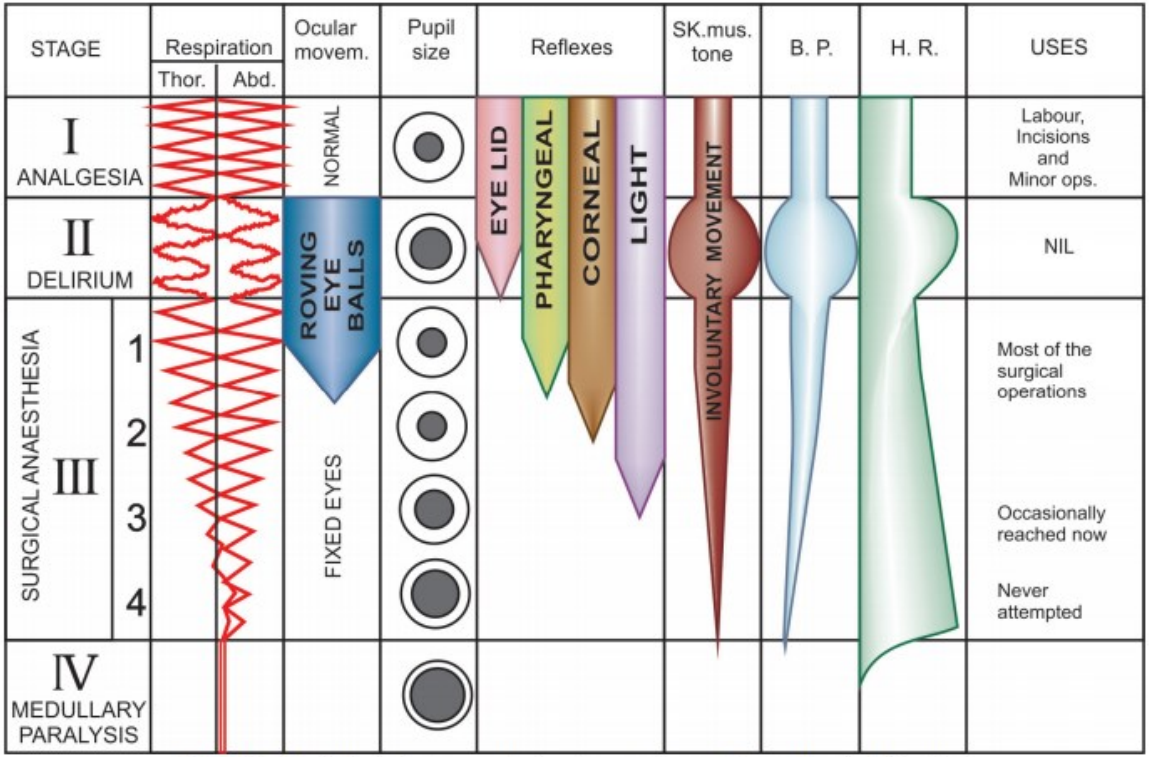


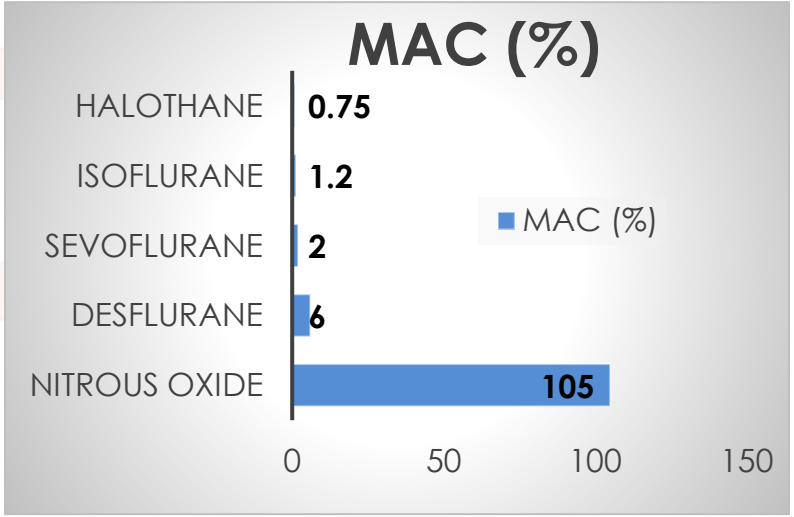
Fig. 27.1: Physiological changes during stages of general anaesthesia (with ether)

Stages of Anaesthesia

Stage I: Analgesia	• Analgesia • Amnesia • Euphoria • Reflexes & Respiration Remain normal
Stage 2: Delirium	• Excitement • Delirium • Combative Behavior • Muscle tone increased • HR & BP rise • Pupil is dilate
Stage 3: Surgical Anesthesia	• Plane 1: Roving eyeballs • Plane 2: Loss of Corneal & Laryngeal reflexes • Plane 3: Pupil starts dilating, loss light reflex • Plane 4: Intercostal paralysis, dilated pupil
Stage 4: Medullary Depression	• Respiratory Arrest • Cardiac Depression/arrest • No eye Movement

General Anaesthetics (GAs)

- General anesthetics (GAs) are drugs which produce reversible loss of all sensation and consciousness.
- **Inhaled GAs:**
  - **A. Gas:** Nitrous oxide
  - **B. Volatile Liquid:** Ether, Halothane, Isoflurane, Desflurane, Sevoflurane



Pharmacology of Inhaled GAs

TABLE 27.1 **Physical and anaesthetic properties of inhalational anaesthetics**

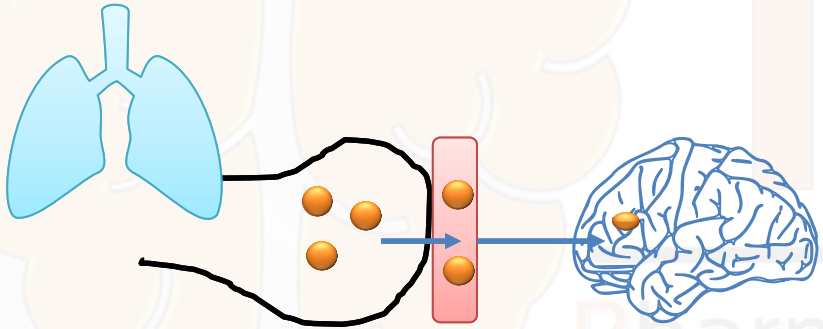
Anaesthetic	*Boiling point (°C)*	*Inflamma-bility*	*Irritancy (odour)*	*Oil: Gas partition coefficient**	*Blood: Gas partition coefficient**	*MAC (%)*	*Induction*	*Muscle relaxation*
1. Ether	35	Infl. + Explo.	+++ (Pungent)	65	12.1	1.9	Slow	V. good
2. Halothane	50	Noninfl.	– (Pleasant)	224	2.3	0.75	Interm.	Fair
3. Isoflurane	48	Noninfl.	± (Unpleasant)	99	1.4	1.2	Interm.	Good
4. Desflurane	24	Noninfl.	+ (Unpleasant)	19	0.42	6.0	Fast	Good
5. Sevoflurane	59	Noninfl.	– (Pleasant)	50	0.68	2.0	Fast	Good
6. Nitrous oxide	Gas	Noninfl.	–	1.4	0.47	105	Fast	Poor

*At 37°C; Oil: gas and blood: gas partition coefficients are measures of solubility of the anaesthetic in lipid and blood respectively.

MAC—Minimal alveolar concentration; Infl.—Inflammable; Explo.—Explosive; Interm.—Intermediate

Pharmacology of Inhaled GAs

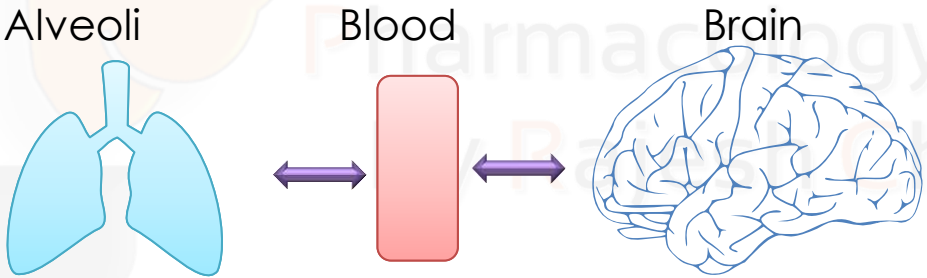
- **Mechanism of Action:** Enhance the inhibitory action (GABA-A Mediated & Glycine Mediated action) and inhibit the Excitatory action (Glutamate & Cation conduction)
- **Pharmacokinetics:**



Pharmacology of Inhaled GAs

Pharmacokinetics:

- Inhaled GAs are gases or vapour & highly lipid solouble, so they rapidly diffuse across pulmonary alveoli and tissue barriers.
- The deepness of anaesthesia depends on potency of GAs and its partial pressure (PP) in the brain, while induction and recovery depend on the rate of change of PP in the brain.
- Transfer of the anaesthetic between lung and brain depends on a series of tension gradients which may be summarized as—



Pharmacology of Inhaled GAs

1. Nitrous Oxide (N_2O):

- It is a colourless, odourless, heavier than air, **noninflammable** gas supplied under pressure in steel cylinders. It is nonirritating, but **low potency** anaesthetic.
- unconsciousness cannot be produced in all individuals without concomitant hypoxia;
- **MAC is 105%** implying that even pure N2O cannot produce adequate anaesthesia at 1 atmosphere pressure.
- Patients maintained on **70% N2O + 30% O2 along with muscle relaxants**
- Nitrous oxide is a good analgesic; even 20% produces analgesia equivalent to that produced by conventional doses of morphine

Pharmacology of Inhaled GAs

1. Nitrous Oxide (N_2O):

- **Muscle relaxation is minimal**. Neuromuscular blockers are mostly required
- Onset of N2O action is **quick and smooth** (but thiopentone is often used for induction), **recovery is rapid**, because of its low blood solubility
- **ADR:**
  - Second gas effect and diffusion hypoxia occur with N2O only.
  - It tends to increase sympathetic tone which counteracts weak direct depressant action on heart and circulation.

Pharmacology of Inhaled GAs

1. Nitrous Oxide (N_2O):

Uses:

- Nitrous oxide is generally used as a carrier and adjuvant to other anaesthetics.
- A mixture of 70% N2O + 25–30% O2 + 0.2–2% another potent anaesthetic is employed for most surgical procedures.

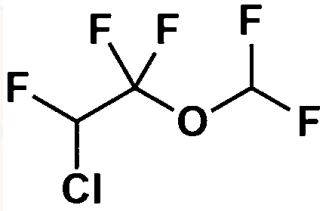
Pharmacology of Inhaled GAs

2. Diethyl Ether (C2H5-O-C2H5):

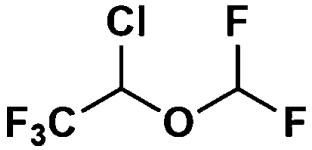
- It is a **highly volatile liquid**, produces **irritating vapors** which are **inflammable** and **explosive**
- Ether is a potent anaesthetic, produces **good analgesia** and marked **muscle relaxation** by reducing ACh output from motor nerve endings
- It is highly soluble in blood. **Induction is prolonged** and unpleasant with struggling, **breathholding**, **salivation** and marked **respiratory secretions** (atropine must be given as premedication to prevent the patient from drowning in his own secretions).
- **Recovery is slow**; **postanaesthetic nausea, vomiting and retching are marked**.

Pharmacology of Inhaled GAs

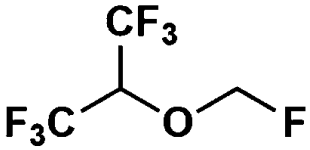
Halogenated Hydrocarbon GAs



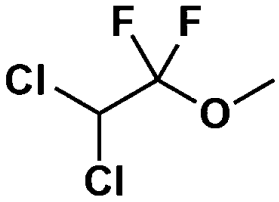
Enflurane



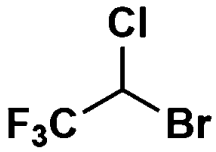
Isoflurane



Sevoflurane



Methoxyflurane



Halothane

Pharmacology of Inhaled GAs

3. Halothane (FLUOTHANE)

- It is a volatile liquid with sweet odour, nonirritant and noninflammable. Solubility in blood is intermediate— induction is reasonably quick and pleasant
- It is a **potent anesthetic** (Require control administration), For **induction 2–4%** and for **maintenance 0.5–1%** is delivered by the use of a special vaporizer
- It is **not a good analgesic or muscle relaxant**, but it potentiates competitive neuromuscular blockers
- Halothane causes **Cardiac depression** by reducing intracellular Ca2+ concentration, Moreover, sympathetic activity fails to increase reflexly
  - BP Fall (20-30 mmHg)
  - Reduced Cardiac output
  - HR reduced

Pharmacology of Inhaled GAs

3. Halothane (FLUOTHANE)

- Respiratory depression, so ventilatory support with added oxygen is frequently required
- Due to ADR and availability of other Gas it is replaced by others

Pharmacokinetic:

- MAC: 0.75%, highly potent
- Blood/Gas Partition Coefficient: 2.4
- Rapid and smooth indiction
- **Metabolism:** 20-40% is metabolized in liver by oxidation, normally excreted in form of **trifluoroacetic acid**, caused hepatotoxicity
- **Clearance**: Around 60-80% is cleared out unchanged by lungs.

Pharmacology of Inhaled GAs

3. Halothane (FLUOTHANE)

Disadvantages/ADR:

- Respiratory depression, Cardiac depression, not a good analgesic or muscle relaxant
- Cardiac arrhythmias, Hypotensive effect
- Hepatotoxic
- Malignant hyperthermia

Therapeutic Uses:

- Anaestehsia along with nitrous oxide, opioids, or local anesthetics
- Halothane is not hepatotoxic in children so safer for child
- Combined with its pleasant odor, it is suitable in pediatrics for inhalation induction, although sevoflurane is now the agent of choice

Intravenous General Anaesthetics (GAs)

- General anesthetics (GAs) are drugs which produce reversible loss of all sensation and consciousness.

Intravenous GAs:

- **A. Fast Acting:** Thiopentone sod., Methohexitone sod., Propofol, Etomidate
- **B. Slow Acting:**
  - **Benzodiazepines** (Diazepam, Lorazepam, Midazolam)
  - **Dissociative anaesthesia** (Ketamine)
  - **Opioid analgesia** (Fentanyl)

Pharmacology of Intravenous GAs

Intravenous GAs:

- **Fast IV** anaesthetics produce loss of consciousness in one arm-brain circulation time (~11 sec) (very rapidly)
- So these are mainly used to induction of anaesthesia because of rapidity of onset of action and for maintenance we can use inhaled Gas

Thiopentone Sodium

- A ultrashort acting thiobarbiturate which mainly act via GABA-A mediated inhibitory action on brain.
- For the anaesthesia: Injected i.v. (3–5 mg/kg) as a 2.5% solution, it produces unconsciousness in 15–20 sec.

Pharmacology of Intravenous GAs

Thiopentone Sodium

- Thiopentone is a poor analgesic, so painful surgery may perform with an opioid or N2O.
- It also a week muscle relaxant.

TABLE 27.2 Effects of intravenous anaesthetics on vital functions

Anaesthetic drug	*HR*	*BP*	*Resp.*	*CBF*
1. Thiopentone	↑↑	↓↓	↓↓	↓↓↓
2. Propofol	–, ↓	↓↓↓	↓↓↓	↓↓↓
3. Etomidate	–	↓	↓	↓↓↓
4. Diazepan	–, ↑	↓	↓↓	↓↓
5. Ketamine	↑↑	↑↑	↓, –	↑↑↑
6. Fentanyl	↓	↓	↓↓↓	↓

HR—Heart rate; BP—Systemic arterial blood pressure; Resp.—Respiratory drive; CBF—Cerebral blood flow. (Changes in intracranial pressure parallel CBF).

Pharmacology of Intravenous GAs

Thiopentone Sodium

Pharmacokinetics:

- Its undissociated (unionized) form has high lipid solubility—enters brain almost instantaneously.
- Initial distribution depends on organ blood flow—brain gets large amounts. Less in muscle and fat
- Blood concentration falls and it back diffuses from the brain: consciousness is regained in 6– 10 min (t½ of distribution phase is 3 min)
- Metabolized by Liver (t1/2- 8-12 hrsz)
- CNS depression may persist for > 12 hr.

Pharmacology of Intravenous GAs

Thiopentone Sodium

ADR:

- Laryngospasm due respiratory secretions or other irritants are present. This can be prevented by atropine premedication and administration of succinylcholine immediately after thiopentone
- Succinylcholine and thiopentone react chemically—should not be mixed in the same syringe
- Shivering and delirium may occur during recovery
- It can precipitate acute intermittent porphyria in susceptible individuals, therefore contraindicated.

Pharmacology of Intravenous GAs

Thiopentone Sodium

Uses:

- Anaesthesia
- rapid control of convulsions

Pharmacology of Intravenous GAs

Propofol

- Presently, propofol is more frequently used over the thiopentone as an i.v. anaesthetic, both for induction as well as maintenance.
- It is an oily liquid employed as a 1% emulsion.
- 15-45 sec required for Unconsciousness
- Propofol distributes rapidly (distribution t½ 2–4 min).
- Elimination t½ (100 min) is much shorter than that of thiopentone due to rapid metabolism.

Pharmacology of Intravenous GAs

BZDs

- BZDs used as both preanesthetic medication and as well as anesthetic agents.
- BZDs are now frequently used for inducing, maintaining and supplementing anaesthesia as well as for 'conscious sedation'.
- Diazepam at 0.2–0.3 mg/kg i.v. injecton produce sedation, amnesia and then unconsciousness in 5–10 min and duration is approx. 1 hr without any other Gas due to redistribution of the drug (distribution t½ of diazepam is 15 min),
- but amnesia persists for 2–3 hr and sedation for 6 hr or more. Recovery is further delayed if larger doses are given.
- BZDs are poor analgesics : an opioid or N2O is usually added if the procedure is painful.

Pharmacology of Intravenous GAs

Ketamine

- A dissociative anesthetic agents
- Block the NMDA receptor mediated excitatory action
- This unique anaesthetic is pharmacologically related to the hallucinogen phencyclidine.
- It induces a so called 'dissociative anaesthesia' characterized by profound analgesia, immobility, amnesia with light sleep
- the patient appears to be dissociated from his body and surroundings for some time after recovery (unable to process sensory stimuli and does not react to them)
- The primary site of action is in the cortex and subcortical areas; not in the reticular activating system, which is the site of action of barbiturates

Preanesthetic Medications

- Preanesthetic medication term applied to the administration of drugs prior to general anaesthesia so as to make anaesthesia safer for the patient. Ensures comfort to the patient & to minimize adverse effects of anaesthesia
- Basic aims are:
- 1. **Relief of anxiety** and apprehension preoperatively and to facilitate smooth induction.
- 2. **Amnesia** for pre- and postoperative events.
- 3. Supplement **analgesic** action of anaesthetics and potentiate them so that less anaesthetic is needed.
- 4. **Decrease secretions** and vagal stimulation that may be caused by the anaesthetic.
- 5. **Antiemetic effect** extending to the postoperative period. 6. Decrease acidity and volume of gastric juice so that it is less damaging if aspirated.

Preanesthetic Medications

- **Anti-Anxiety**: Benzodiazepens, diazepam (5–10 mg oral) or lorazepam (2 mg oral or 0.05 mg/kg i.m. 1 hour before).
  - They provide smooth induction
  - Also produce Amnesia (in lorazepam)
  - Midazolam shows good analgesic action too
  - BZDs show respiratory depression or accentuation of postoperative vomiting
  - They avoided co-administration with morphine, pethidine
- **Promethazine** (25mg i.m.) has sedative, antiemetic & anticholinergic action - Causes negligible respiratory depression & suitable for children

Preanesthetic Medications

- **Analgesics**
- Morphine (10 mg) or pethidine (50–100 mg), i.m.
- They have analgesic properties as well as anti-anxiety
- apprehension of the operation, produce pre- and postoperative analgesia, smoothen induction, reduce the dose of anaesthetic required and supplement poor analgesics (thiopentone, halothane) or weak anaesthetics (N2O).
- Postoperative restlessness is also reduced co-administration with morphine, pethidine
- ADR: They depress respiration, interfere with pupillary signs of anaesthesia, may cause fall in BP during anaesthesia, can precipitate asthma and tend to delay recovery.

Preanesthetic Medications

- **Antisecretory**
- **1. Anticholinergic**
- Atropine or hyoscine (0.6 mg or 10–20 µg/kg i.m./i.v.) or glycopyrrolate (0.2–0.3 mg or 5–10 µg/kg i.m./ i.v.) have been used, primarily to reduce salivary and bronchial secretions
- **2. AntiGastric**
- Ranitidine (150 mg)/famotidine (20 mg) or omeprazole (20 mg)/pantoprazole (40 mg) given night before and in the morning benefit by raising pH of gastric juice and may also reduce its volume.

Preanesthetic Medications

- **Antiemetics**
- Metoclopramide (10mg i.m.) used as antiemetic & as prokinetic gastric emptying agent prior to emergency surgery.
- Domperidone (10mg oral) more preferred (does not produce extrapyramidal side effects)
- Ondansetron (4-8mg i.v.), a 5HT3 receptor antagonist, found effective in preventing post-anaesthetic nausea & vomiting

PC
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By Rajesh Choudhary

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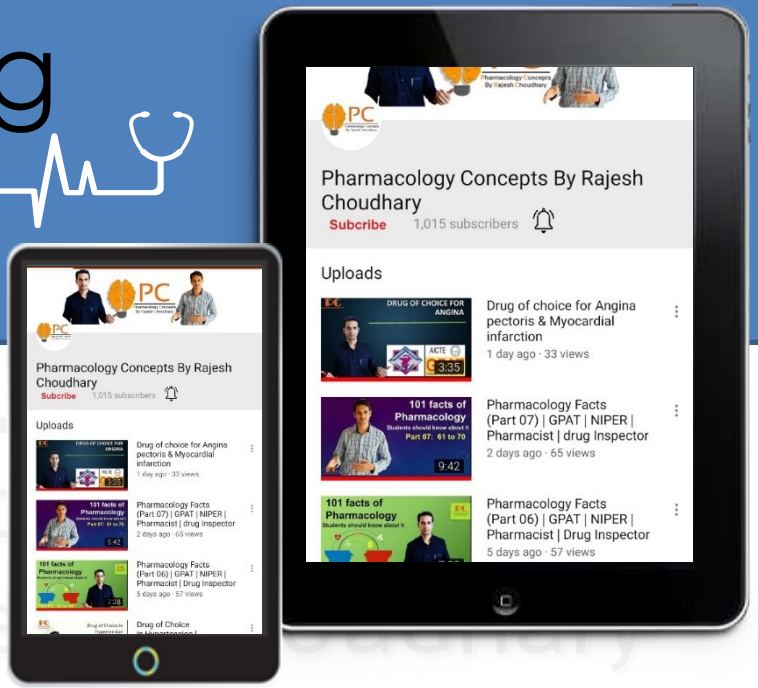

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