GENERAL ANESTHATIC DRUGS

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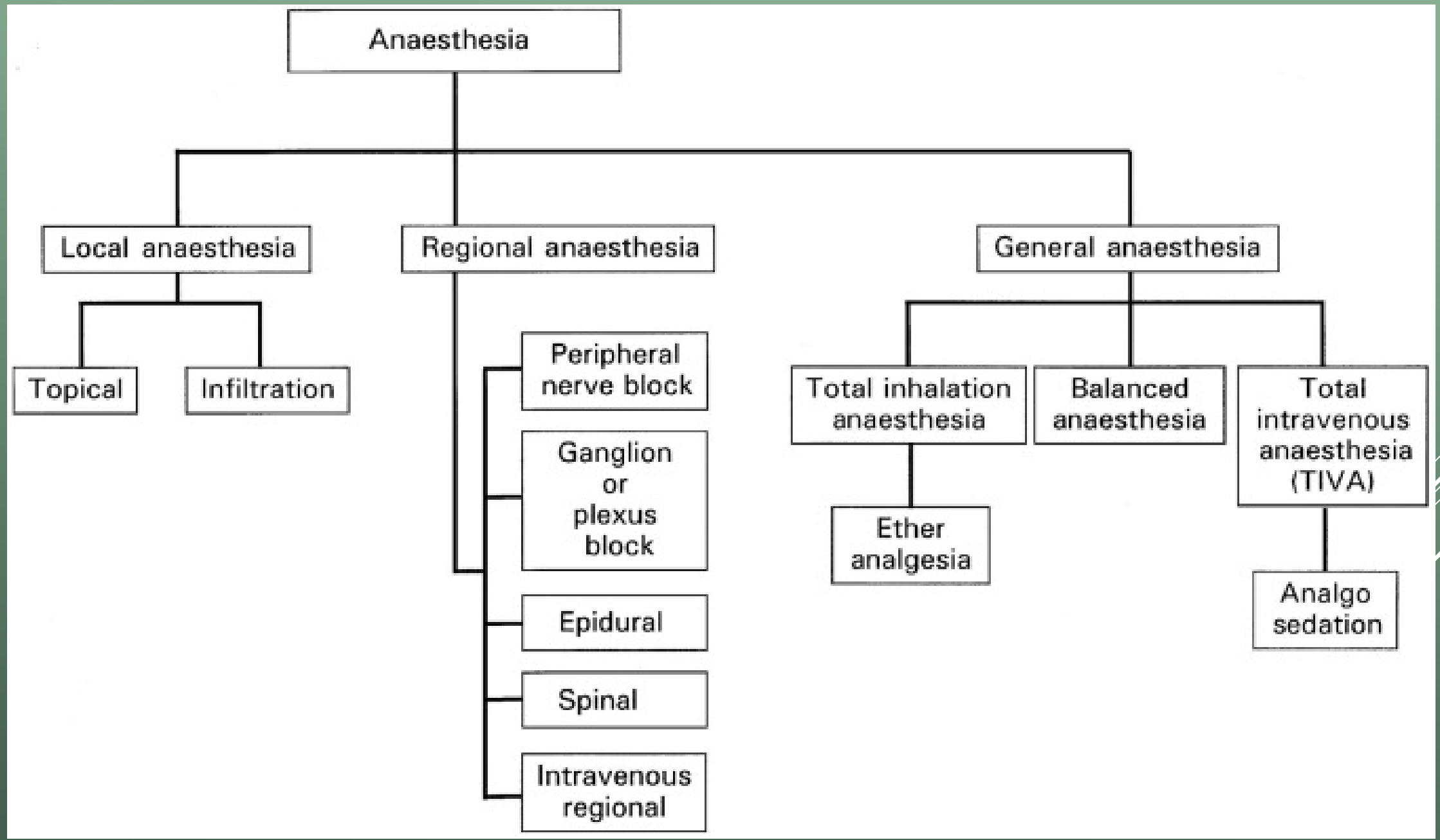
PHASES OF ANESTHESIA

- Induction: putting the patient to sleep
- Maintenance: keeping the patient asleep (without awareness)
- Emergence: waking the patient up (recovery)


Anaesthesia
Local anaesthesia
Regional anaesthesia
General anaesthesia
Topical
Infiltration
Peripheral nerve block
Ganglion or plexus block
Epidural
Spinal
Intravenous regional
Total inhalation anaesthesia
Balanced anaesthesia
Total intravenous anaesthesia (TIVA)
Ether analgesia
Analgo sedation

Balanced Anesthesia

The practice of using combinations of agents, each for a specific purpose, is what is termed "balanced anesthesia".

An example of a balanced technique would be the use of

- Propofol for "induction"
- Isoflurane and N_2O for "Maintenance"
- Fentanyl for "Analgesia"
- Rocuronium for "muscle relaxation"

Rocuronium bromide (brand names Zemuron, Esmeron) is an aminosteroid non-depolarizing neuromuscular blocker or muscle relaxant used in modern anaesthesia to facilitate tracheal intubation by providing skeletal muscle relaxation, most commonly required for surgery or mechanical ventilation. Each ml of solution for injection / infusion contains 10 mg rocuronium bromide. Each vial with 2.5 ml contains 25 mg rocuronium bromide.

- Fentanyl is a powerful synthetic opioid analgesic that is similar to morphine but is 50 to 100 times more potent, and it is typically used to treat patients with severe pain or to manage pain after surgery. It is also sometimes used to treat patients with chronic pain who are physically tolerant to other opioids. In its prescription form, fentanyl is known by such names as Actiq®, Duragesic®, and Sublimaze®.

ANESTHETICS AND ANESTHETICADJUNCTS

- Analgesics [Opiates, fentanyl (Sublimaze)]
- General depressants

a. Benzodiazepines [benzodiazepines midazolam (Versed)]

b. Barbiturates[secobarbital]

- Neuroleptics [droperidol (Inapsine)] .
- Muscarinic blockers (atropine, scopolomine, glycopyrate) .
- Neuromuscular blockers (paralytics) .
- Miscellaneous Agents(antagonists: naloxone, flumazanil, neostigmine)

ANALGESICS

- Analgesics
- Used with anesthesia to provide analgesia.
- Important ADRs: respiratory depression, cardiovascular depression.
- Potent Analgesics (opiates): morphine, fentanyl, nalbuphine, alfentanil, sufentanil.

❖ Sublimaze® 50 micrograms/ml solution for injection or infusion Fentanyl citrate This medicine contains Fentanyl Citrate, which is an opioid, which can cause addiction. You can get withdrawal symptoms if you stop taking it suddenly.

PRE-ANESTHETIC DEPRESSANTS •

- Benzodiazepines:diazepam, lorazepam, midazolam .
- Barbiturates: secobarbital, pentobarbital
- Mechanism - enhancement of GABA action.

❖ Benzodiazepines are depressants that enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABAA receptor, resulting in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant properties. High doses of many shorter-acting benzodiazepines may also cause anterograde amnesia and dissociation. These properties make benzodiazepines useful in treating anxiety, panic disorder, insomnia, agitation, seizures, muscle spasms, alcohol withdrawal and as a premedication for medical or dental procedures.

❖ Barbiturates are medications that cause you to relax or feel drowsy. They can also stop or prevent convulsions and seizures. The most common uses are for anesthesia reasons, treating epilepsy and nonepileptic seizures, insomnia and other conditions.

Barbiturates belong to the sedative-hypnotic class of medications. Barbiturates affect your brain by increasing a brain chemical called gamma-aminobutyric acid (GABA), which slows down the activity of your brain cells

NEUROLEPTICS

- Antipsychotic agents: droperidol .
- Produces a trance-like state, for neuroleptic anesthesia.
- Effective antiemetics

Neuroleptics, also known as antipsychotic medications, are used to treat and manage symptoms of many psychiatric disorders. They fall into two classes: first-generation or "typical" antipsychotics and second-generation or "atypical" antipsychotics." Neuroleptic drugs block dopamine receptors in the nervous system.

- Droperidol is a butyrophenone derivative and dopamine antagonist used to prevent and treat postoperative nausea and vomiting.

- droperidol (Rx)
- Brand and Other Names:Inapsine
- Classes: Antiemetic Agents
- Antiemetic
- Initial: No more than 2.5 mg IV/IM; additional doses of 1.25 mg may be given if benefit outweighs potential risk

MISCELLANEOUS DRUGS

- Anticholinergic agents: atropine, scopolamine, glycopyrrolate.
- Use to reduce secretions.

MIDAZOLAM

- Midazolam is a short-acting benzodiazepine.
- Midazolam is used for conscious sedation, anxiolysis, and amnesia during minor surgical or diagnostic procedures.
- Midazolam is used as an inducing agent, and as an adjunct to regional anesthesia.
- Midazolam, as other benzodiazepines (BDZs) act at limbic, thalamic, and hypothalamic structures producing a dose dependant CNS depression including sedation, hypnosis, skeletal muscle relaxation, and anticonvulsant activity.
- BDZs act by potentiating the action of GABA at GABAA receptors. Benzodiazepines cause allosteric modulation of GABAA receptor complex, but do not activate the channel. • Unlike barbiturates which augment GABA responses by increasing the length of time that chloride channels remain open, BDZs enhance GABA efficacy by increasing the affinity of GABA to its binding site on the GABAA receptor.

❖ Preoperative Sedation/Anxiolysis With Anterograde Amnesia

❑ IM

70-80 mcg/kg (dose range ~5 mg) 30-60 minutes before surgery (reduce 50% for chronically ill or geriatric patients)

❑ IV

Initial: Usually 0.5-1 mg given over 2 minutes (not to exceed 2.5 mg/dose); wait 2-3 minutes to evaluate sedative effect after each dose adjustment; total dose >5 mg usually not necessary to reach desired sedation; use 30% less midazolam if patient premedicated with narcotics or other CNS depressants

What are the Drugs used as GA ? (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
  1. **Benzodiazepines (slower acting):**
     - Diazepam, Lorazepam, Midazolam
  1. **Dissociative anaesthesia:**
     - Ketamine
  1. **Neurolept analgesia:**
     - Fentanyl

DIETHYL ETHER (C2H5 – O – C2H5)

- **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

❑ 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.
- Struggling, breath holding.
- salivation and secretions (drowning) atropine.
- Slow recovery – nausea & vomiting
- Cardiac arrest.
- Convulsion in children.
- Cross tolerance – ethyl alcohol.

HALOTHANE

- Fluorinated volatile liquid with sweet odour,
- non-irritant non-inflammable and supplied in amber coloured bottle
- Potent anaesthetic (if precise control), 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 •
- Delivered by the use of a special vapourizer
- Not good analgesic or relaxants
- Potentiates NM blockers

❖ Mechanism of action

Halothane causes general anaethesia due to its actions on multiple ion channels, which ultimately depresses nerve conduction, breathing, cardiac contractility. Its immobilizing effects have been attributed to its binding to potassium channels in cholinergic neurons. Halothane's effect are also likely due to binding to NMDA and calcium channels, causing hyperpolarization

DOSAGE AND ADMINISTRATION

Fluothane (halothane) may be administered by the nonrebreathing technique, partial rebreathing, or closed technique. The induction dose varies from patient to patient but is usually within the range of 0.5% to 3%. The maintenance dose varies from 0.5% to 1.5%.

HALOTHANE (PROTOTYPE)

Advantages

- Potent anesthetic, rapid induction & recovery
- Neither flammable nor explosive.
- sweet smell, non irritant
- Does not augment bronchial and salivary secretions.
- Low incidence of postoperative nausea and vomiting.
- Relaxes both skeletal and uterine muscle, and can be used in obstetrics when uterine relaxation is indicated.
- Not hepatotoxic in pediatric patient, and combined with its pleasant odor, this makes it suitable in children for inhalation induction.

HALOTHANE : DISADVANTAGES:

- Weak analgesic (thus is usually coadministerd with N2O, opioids)
- Is a strong respiratory depressant.
- Is a strong cardiovascular depressant; halothane is vagomimetic and cause atropine-sensitive bradycardia.
- Cardiac arrhythmias: serious if hypercapnia develops due to hypoventilation and an increase in the plasma concentration of catecholamines)
- Hypotensive effect (phenylephrine recommended)
- Hepatotoxic: is oxidatively metabolized in the liver to tissue-toxic hydrocarbons (e.g., trifluroethanol and bromide ion).
- Malignant hyperthermia

ENFLURANE

- **Advantages:**
- Less potent than halothane, but produces rapid induction and recovery
- ~2% metabolized to fluoride ion, which is excreted by the kidney
- Has some analgesic activity
- Differences from halothane:

1. Fewer arrhythmias,
2. less sensitization of the heart to catecholamines,
3. and greater potentiation of muscle relaxant due to more potent “curare-like” effect. ((Curare, drug belonging to the alkaloid family of organic compounds, derivatives of which are used in modern medicine primarily as skeletal muscle relaxants, being administered concomitantly with general anesthesia for certain types of surgeries, particularly those of the chest and the abdomen.))

- **Disadvantages**: CNS excitation at twice the MAC. Can induce seizure

ISOFLURANE

- **Advantages**
- A very stable molecule that undergoes little metabolism.
- Not tissue toxic.
- Does not induce cardiac arrhythmias.
- Does not sensitize the heart to the action of catecholamines.
- Produces concentration-dependent hypotension due to peripheral vasodilation.
- Also dilates the coronary vasculature, increasing coronary blood flow and oxygen consumption by the myocardium, this property may make it beneficial in patients with IHD (Ischemic heart disease).

Mechanism of Action

Induction and maintenance of general anesthesia are achieved through various sites of action. The most likely of these sites include inhibition of neurotransmitter-gated ion channels such as GABA, glycine, and N-methyl-d-aspartate (NMDA) receptors in the central nervous system (CNS). Inhibition of these receptors helps to produce the amnesia and sedation needed for adequate surgical conditions. Volatile anesthetics in general also have sites of action within the spinal cord that contribute to skeletal muscle relaxation through inhibition of NMDA-type glutamate and glycine receptors.

- Administration
- Administration of volatile anesthetics, including isoflurane, is based on each agent's individual minimum alveolar concentration (MAC), which is used as a surrogate for the partial pressure of each agent in the brain. MAC is then defined as the alveolar concentration needed to prevent movement in 50% of patients in response to surgical incision. MAC is based on the agent's partial pressure relative to the atmospheric pressure. At sea level, the MAC of isoflurane is 1.2%, which can otherwise be stated as 1 MAC of isoflurane

❑ Desflurane:

Rapidity of induction and recovery: outpatient surgery.

- Less volatility (must be delivered using a special vaporizer).
- Like isoflurane, it decreases vascular resistance and perfuse all major tissues very well.
- Irritating cause apnea, laryngospasm, coughing, and excessive secretions.

❑ Sevoflurane:

- Has low pungency, not irritating the airway during induction; making it suitable for induction in children
- Rapid onset and recovery:
- Metabolized by liver, releasing fluoride ions; thus, like enflurane, it may prove to be nephrotoxic.

❑ Methoxyflurane

- The most potent and the best analgesic anesthetic available for clinical use. Nephrotoxic and thus seldom used.

NITROUS OXIDE (N2O) “LAUGHING GAS”

- It is a potent analgesic but a weak general anesthetic.
- Rapid onset and recovery:
- Does not depress respiration, and no muscle relaxation.
- Clinical use: dental surgery, obstetrics, postoperative physiotherapy, refractory pain in terminal illness, and maintenance of anesthesia.
- The least hepatotoxic, Teratogenic, bone marrow depression.
- N2O can concentrate the halogenated anesthetics in the alveoli when they are concomitantly administered because of its fast uptake from the alveolar gas.
- Diffusion hypoxia: speed of N2O movement allows it to retard oxygen uptake during recovery.

NITROUS OXIDE

❑ Advantages:

- ❖ Non-inflammable and nonirritant
- ❖ Rapid induction and recovery
- ❖ Very potent analgesic (low concentration)
- ❖ No effect on heart rate and respiration
- ❖ No nausea and vomiting – post anaesthetic not marked
- ❖ Nontoxic to liver, kidney and brain

❑ Disadvantages:

- ❖ Not potent alone (supplementation)
- ❖ Not good muscle relaxant,
- ❖ Hypoxia, unconsciousness cannot be produced without hypoxia
- ❖ Inhibits methionine synthetase (precursor to DNA synthesis)
- ❖ Inhibits vitamin B-12 metabolism
- ❖ Dentists, OR personnel, abusers at risk
- ❖ Gas filled spaces expansion (pneumothorax) – dangerous

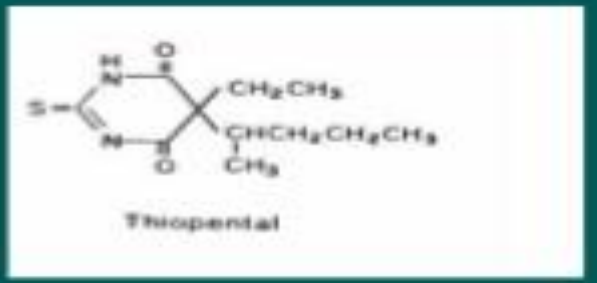
Intravenous Anaesthetics:

- 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:



- 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)

WHAT ARE BARBITURATES?

- Barbiturates are a class of drugs that were used extensively in the 1960s and 1970s as a treatment for anxiety, insomnia, and seizure disorders. Apart from a few specific indications, they are not commonly prescribed these days, having been largely superseded by benzodiazepines, which are much safer, although still potentially addictive.

- Barbiturates are known as central nervous system depressants. They enhance the action of GABA, a neurotransmitter that inhibits the activity of nerve cells in the brain.

BARBITURATES • THIOPENTAL & METHOHEXITAL .CONTD

Barbiturates

• Thiopental & methohexital are highly lipid soluble & can produce unconsciousness & surgical anesthesia in <1 min.

• Rx: induction of anesthesia & short procedures

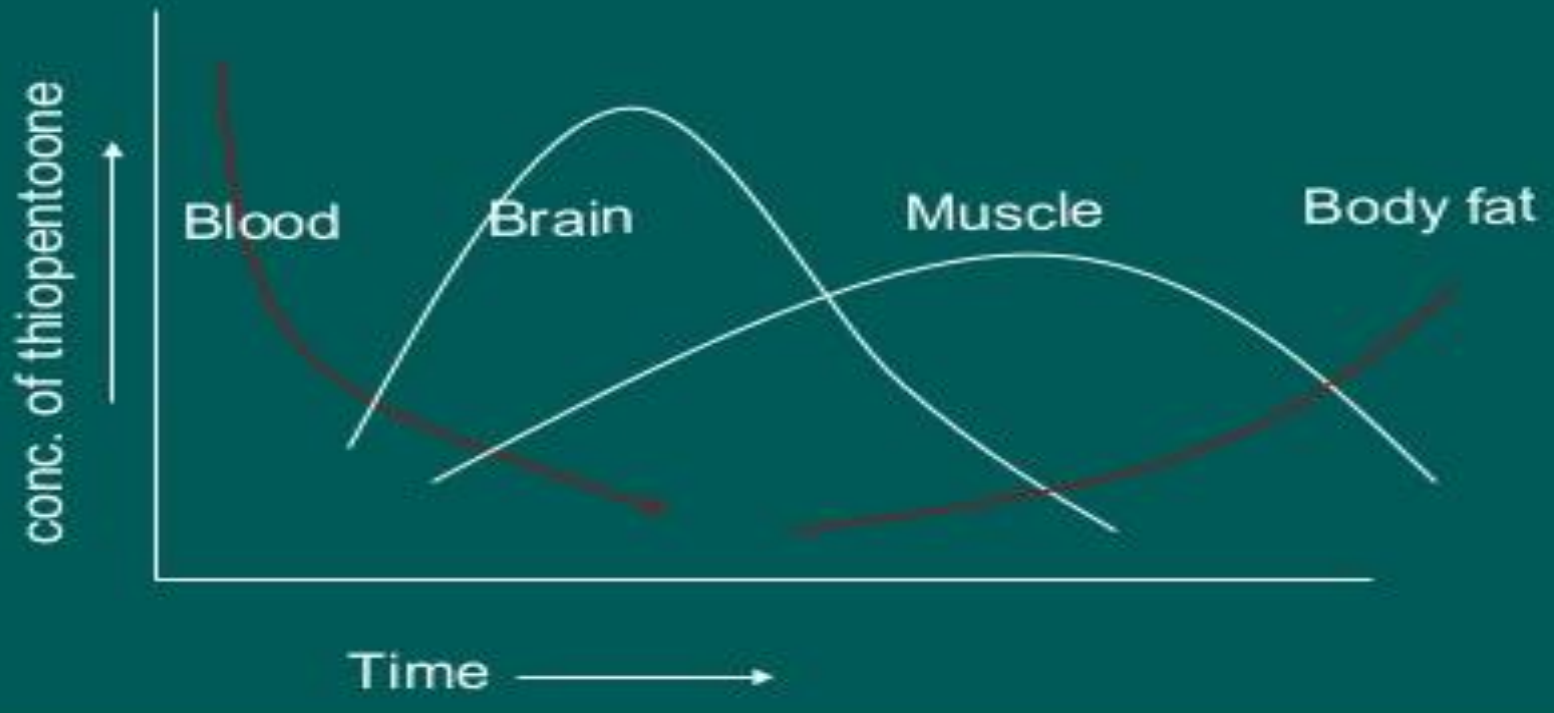
• Actions are terminated by redistribution

• With single bolus - emergence from GA occurs in ~ 10 mins

• Hepatic metabolism is required for elimination

Tiopentone – contd,.

Redistribution:



INTRAVENOUS ANESTHETICS

- **Barbiturates (thiopental, methohexital)**
- Potent anesthetic but a weak analgesic
- High lipid solubility; quickly enter the CNS and depress function, often in less than one minute, and redistribution occur very rapidly as well to other body tissues, including skeletal muscle and ultimately adipose tissue (serve as a reservoir).
- Thiopental may cause sever hypotension in hypovolemic or shock patient
- All barbiturates can cause apnea, coughing, chest wall spasm, laryngospasm, and bronchospasm

INTRAVENOUS ANESTHETICS/ PROPOFOL

What is propofol?

- Propofol (Diprivan) slows the activity of your brain and nervous system.
- Propofol is used to put you to sleep and keep you asleep during general anesthesia for surgery or other medical procedures. It is used in adults as well as children 2 months and older.
- Propofol is also used to sedate a patient who is under critical care and needs a mechanical ventilator (breathing machine).
- Propofol, Phenol derivative, It is an IV sedative-hypnotic used in the induction and or maintenance of anesthesia.

INTRAVENOUS ANESTHETICS/ PROPOFOL / / CONT.

- Onset is smooth and rapid (40 seconds)
- It is occasionally accompanied by excitatory phenomena, such as muscle twitching, spontaneous movement, or hiccups.
- Decrease BP without depressing the myocardium, it also reduce intracranial pressure.
- It is widely used and has replaced thiopental as the first choice for anesthesia induction and sedation, because it produces a euphoric feeling in the patient and does not cause post anesthetic nausea and vomiting
- 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
- Poor analgesia

INTRAVENOUS ANESTHETICS/ ETOMIDATE

Brand Names : Amidate

Generic Name : Etomidate

Indication : Used in the induction of general anesthesia.

Associated Therapies : General Anesthesia

Is used to induce anesthesia, it is a hypnotic agent but lacks analgesic activity.

- Induction is rapid, short acting
- No effect on heart and circulation. Thus it is only used for patients with coronary artery disease or cardiovascular dysfunction,
- **Mechanism of action : Etomidate binds at a distinct binding site associated with a Cl- ionopore at the GABAA receptor, increasing the duration of time for which the Cl- ionopore is open. The post-synaptic inhibitory effect of GABA in the thalamus is, therefore, prolonged.**
- Adverse effects: a decrease in plasma cortisol and aldosterone levels which can persist for up to eight hours. This is due to inhibition of 11- B-hydroxylase

INTRAVENOUS ANESTHETICS/ KETAMINE

Brand Names : Ketalar

Generic Name : Ketamine

Ketamine (phencyclidine derivative) a short- acting, anesthetic, induces a dissociated state in which the patient is unconscious (but may appear to be awake) and does not feel pain.

- This dissociative anesthesia provides sedation, amnesia, and immobility.
- Ketamine stimulates central sympathetic outflow, causing stimulation of the heart with increased blood pressure and CO. It is also a potent bronchodilator.
- Therefore, it is beneficial in patients with hypovolemic or cardiogenic shock and in asthmatics. Conversely, it is contraindicated in hypertensive or stroke patients.
- Ketamine is used mainly in children and elderly adults for short procedures.
- It is not widely used, because it increases cerebral blood flow and may induce hallucinations, particularly in young adults.

INTRAVENOUS ANESTHETICS/ KETAMINE / CONT.

- Ketamine is indicated as an anesthetic agent for recommended diagnostic and surgical procedures. If skeletal muscle relaxation is needed, it should be combined with a muscle relaxant. If the surgical procedure involves visceral pain, it should be supplemented with an agent that obtunds visceral pain. Ketamine can be used for induction of anesthesia prior other general anesthetic agents and as a supplement of low potency agents.
- Reports have indicated a potential use of ketamine as a therapeutic tool for the management of depression when administered in lower doses.

- **Mechanism of action Ketamine interacts with N-methyl-D-aspartate (NMDA) receptors, opioid receptors, monoaminergic receptors, muscarinic receptors and voltage sensitive Ca ion channels. Unlike other general anaesthetic agents, ketamine does not interact with GABA receptors.**

DEXMEDETOMIDINE

- Brand Names : Dexdor, Precedex
- Generic Name : Dexmedetomidine
- Dexmedetomidine is an alpha-2 agonist used for sedation during various procedures, in intensive care settings and surgery.
- It is relatively unique in its ability to provide sedation without respiratory depression.
- Like clonidine, it is an α2 receptor agonist in certain parts of the brain. Dexmedetomidine has sedative, analgesic, sympatholytic, and anxiolytic effects that blunt many cardiovascular responses.
- It reduces volatile anesthetic, sedative, and analgesic requirements without causing significant respiratory depression.

DEXMEDETOMIDINE / CONT.

- Indication : For sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting, also used in pain relief; anxiety reduction and analgesia.

- **Mechanism of action : Dexmedetomidine is a specific and selective alpha-2 adrenoceptor agonist. By binding to the presynaptic alpha-2 adrenoceptors, it inhibits the release if norepinephrine, therefore, terminate the propagation of pain signals. Activation of the postsynaptic alpha-2 adrenoceptors inhibits the sympathetic activity decreases blood pressure and heart rate.**

FENTANYL

- Brand Names : Abstral, Actiq, Duragesic, Effentora, Fentora, Instanyl, Lazanda, Sublimaze, Subsys
- Generic Name : Fentanyl
- Street Names
- Apace, China Girl, China Town, China White, Dance Fever, Goodfellas, Great Bear, He-Man, Poison and Tango & Cash,
- Fentanyl, also spelled fentanil, is a powerful opioid used as a pain medication and, together with other medications, for anesthesia.
- Fentanyl is a synthetic opioid that is 80-100 times stronger than morphine. Pharmaceutical fentanyl was developed for pain management treatment of cancer patients, applied in a patch on the skin. Because of its powerful opioid properties, Fentanyl is also diverted for abuse. Fentanyl is added to heroin to increase its potency, or be disguised as highly potent heroin. Many users believe that they are purchasing heroin and actually don’t know that they are purchasing fentanyl – which often results in overdose deaths.

FENTANYL

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 (encourage to breathe)
- Increase tone of chest muscle (muscle relaxant added to mechanical ventilation)
- Nausea, vomiting and itching during recovery
- Naloxone
- Neurolept anaesthesia:

  Combination with Droperidol — fall in BP, arrhythmia and respiratory depression