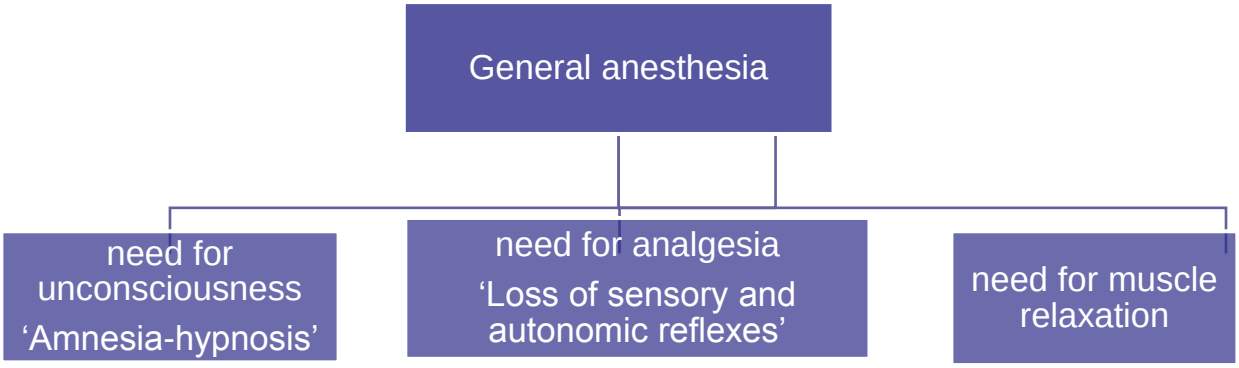
General anesthesia

General anaesthetics (GAs): are drugs which produce reversible loss of all sensations and consciousness. It usually involves a loss of memory and awareness with insensitivity to painful stimuli, during a surgical procedure.



Properties of an ideal anaesthetic:

An ideal anesthetic produces rapid induction & rapid recovery, has wide margin of safety, non-irritant, not inflammable, nor explosive, produce analgesia & skeletal muscles relaxation & no unpleasant taste. Also, It should be cheap, stable (It should not react with rubber tubing) and easily stored.

Signs & stages of anaesthesia (GUEDEL'S Signs) :

Guedel (1920) described four stages with diethyl ether anaesthesia:

A. Stage 1: Analgesia

In stage 1, the patient has decreased awareness of pain, sometimes with amnesia. Consciousness may be impaired but is not lost.

B. Stage 2: Excitement/ Delirium

In stage 2, the patient appears to be delirious and excited. Amnesia occurs, reflexes are enhanced, and respiration is typically irregular; retching and incontinence may occur.

C. Stage 3: Surgical Anesthesia

In stage 3, the patient is unconscious and has no pain reflexes; respiration is very regular, and blood pressure is maintained.

D. Stage 4: Medullary Depression

In stage 4, the patient develops severe respiratory and cardiovascular depression that requires mechanical and pharmacologic support.

MECHANISMS OF ACTION:

The mechanisms of action of general anesthetics are varied. Inhaled anesthetics, barbiturates; benzodiazepines, etomidate, and propofol facilitate γ-aminobutyric acid (GABA)-mediated inhibition at $GABA_A$ receptors.in contrast, sedative benzodiazepines that lack general anesthetic properties (e.g. lorazepam) facilitate GABA action but have no direct actions on $GABA_A$ receptors even at high concentrations. Ketamine does not produce its effects via facilitation of $GABA_A$ receptor functions, but possibly via its antagonism of the action of the excitatory neurotransmitter glutamic acid on the ***N*-methyl-D- aspartate** (NMDA) receptor. This receptor may also be a target for nitrous oxide.

Balanced Anesthesia:

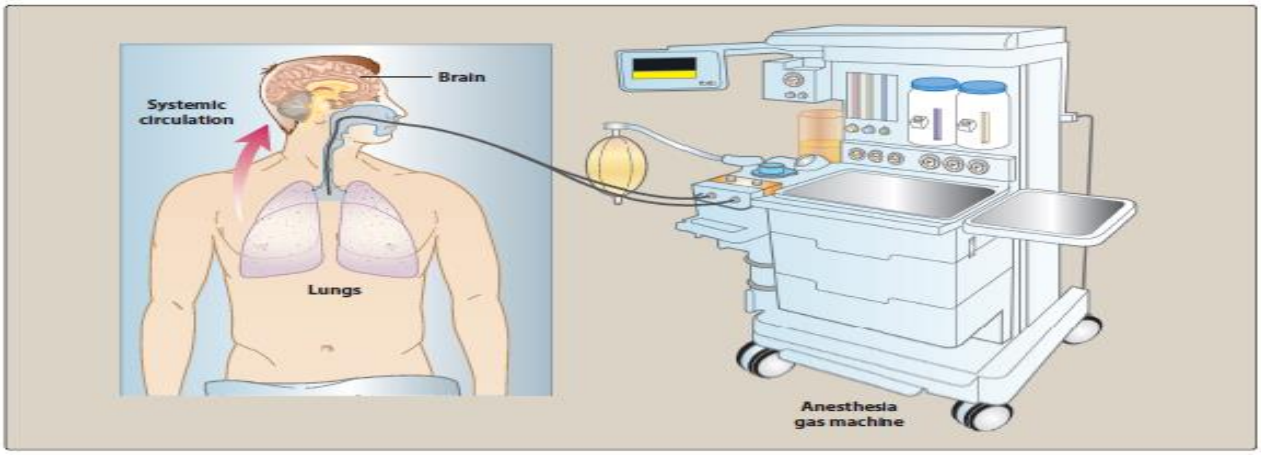
Balanced anesthesia - it is a term used to describe the multidrug approach to managing the patient needs. Balanced anesthesia takes advantage of drug's beneficial effects while minimizing each agent's adverse qualities. So a 'balanced anesthesia' is achieved by a combination of I.V and inhaled anesthesia and Preanesthetic medications.

Preanesthetic medications:

Commonly, patients receive one or more of these preanesthetic medications: H2 blockers (famotidine, ranitidine) to reduce gastric acidity; benzodiazepines (midazolam, diazepam) to allay anxiety and facilitate amnesia; non opioids (acetaminophen, celecoxib) or opioids (fentanyl) for analgesia; antihistamines (diphenhydramine) to prevent allergic reactions; antiemetics (ondansetron) to prevent nausea; and/or anticholinergics (glycopyrrolate) to prevent bradycardia and secretion of fluids into the respiratory tract. Premedications facilitate smooth induction of anesthesia and lower required anesthetic doses. However, they can also enhance undesirable anesthetic effects (hypoventilation) and, when coadministered, may produce negative effects not observed when given individually.

Types of general anesthesia:

1- **Inhaled anesthesia:** Modern inhalation anesthetics are nonflammable, non-explosive Agents, including **nitrous oxide** (gas) and volatile, halogenated hydrocarbons.
The onset of action of anesthetic depends on its solubility in blood, thus:
• N2O has low solubility & rapid onset, while
• Methoxyflurane has high solubility & delayed onset.



A- **Halothane:** has intermediate onset and recovery. It cause hypotension, bradycardia, arrhythmia, respiratory depression & may cause hepatitis.

B- **Isoflurane:** medium rate of onset & recovery. It is used for induction & maintenance of anesthesia.

C- **Desflurane:** has pungent smell with poor induction but rapid recovery.it should be avoided in surgical anesthesia & not used in pediatric surgery. It can cause seizures, cough & laryngeal spasm.

D- **Enflurane:** induction & recovery from anesthesia are rapid. Enflurane may produce mild stimulation of respiratory & bronchial secretions when used alone. Hypotension may occur when anesthesia deepens.

E- **Methoxyflurane:** a volatile liquid provides analgesia & anesthesia. It is used in combination with nitrous oxide but may also be used alone & a skeletal muscle relaxant may be required.

F- **Sevoflurane:** unstable compound with rapid onset and very rapid recovery & short duration of action, this type considered as an ideal agent in anesthesia. It can be used in pediatrics & out patients.

G- **Diethyl ether**: has pungent smell, flammable, explosive. It causes cough & laryngeal spasm.

H- **Nitrous oxide:** Nitrous oxide ("laughing gas") is a nonirritating potent analgesic but a weak general anesthetic. It is frequently used at concentrations of 30 to 50% in combination with oxygen for analgesia, particularly in dentistry. Nitrous oxide alone cannot produce surgical anesthesia, but it is commonly combined with other more potent agents.

Organ System Effects of Inhaled Anesthetics:

Cardiovascular Effects: Most inhaled anesthetics decrease arterial blood pressure moderately. Enflurane and halothane are myocardial depressants that decrease cardiac output, whereas isoflurane, desflurane, and sevoflurane cause peripheral vasodilation. Nitrous oxide is less likely to lower blood pressure than other inhaled anesthetics. Old anesthetics (diethyl ether) cause no change in BP.

Effect on the heart:

Halothane causes bradycardia, sevoflurane have slight effect on the heart, isoflurane & desflurane increase heart rate.

Respiratory Effects:

With the exception of nitrous oxide, all inhaled anesthetics in current use cause a dose dependent decrease in tidal volume and an increase in respiratory rate. All volatile anesthetics are respiratory depressants, as indicated by a reduced response to increased levels of carbon dioxide. The bronchodilating action of halothane and sevoflurane makes them the induction agents of choice in patients with underlying airway problems (e.g. asthma, bronchitis, chronic obstructive pulmonary disease).

CNS effects:

Inhaled anesthetics decrease brain metabolic rate. They reduce vascular resistance and thus increase cerebral blood flow. This may lead to an increase in intracranial pressure. The increase in cerebral blood flow is clinically undesirable in patients who have increased intracranial pressure because of a brain tumor or head injury. Of the inhaled anesthesia, nitrous oxide is the least likely to increase cerebral blood flow.

Renal Effects: depending on the concentration, volatile anesthetics decrease the glomerular filtration rate & renal blood flow.

Hepatic Effects: Volatile anesthetics cause a concentration-dependent decrease in portal vein blood flow,

Effects on Uterine Smooth Muscle: Nitrous oxide appears to have little effect on uterine musculature. However, the halogenated anesthetics are potent uterine muscle relaxants and produce this effect in a concentration-dependent fashion.

Toxicity:

- ✓ Halothane is hepatotoxic.
- ✓ Methoxyflurane and sevoflurane are nephrotoxic.
- ✓ Also the inhaled anesthetics may cause the malignant hyperthermia syndrome which consists of rapid onset of tachycardia and hypertension, sever muscle rigidity,

hyperthermia, hyperkalemia & acid –base imbalance with acidosis. It is a rare but important cause of anesthetic morbidity & mortality. Prolonged exposure to nitrous oxide can cause megaloplastic anemia.

2- Intravenous anesthetic agents:

Advantages:

a. Easy b. Rapid induction & recovery

c. No irritation of respiratory tract

d. No sensitization of heart to catecholamines e. No post-operative nausea or vomiting

f. No explosive hazards

Disadvantages: Once injected, cannot be withdrawn

A- Ultra-short acting barbiturates:

Among the barbiturates three compounds, **Thiopental, methohexital & thiamylal** are useful as induction agents or as subliminal drugs only during short periods when surgery requires increases depth of anesthesia, or as maintenance hypnotics for short surgical procedures.

Thiopental remains the most popular I.V induction agent due to its rapid and pleasant induction of anesthesia. Also, it does not induce obstructive secretions in the airways reduces little or no emesis, and dose not sensitize the myocardium to endogenous catecholamine that may be released in response to the stress of surgery. It can, however, cause cardiovascular depression.

Adverse effects:

Cardiovascular depression, laryngospasm, arterial thrombosis, vasospasm, local ischemia.

Contraindication:

This drug should be avoided in hypotension, sever C.V diseases, apnea, chronic pulmonary disease, status asthmaticus, myxedema, Addison disease, hepatic dysfunction & porphyria.

B- Benzodiazepines: are useful as orally administered premedication, they are also used intravenously in doses that produce conscious sedation rather than hypnosis. The most commonly used is *midazolam. Diazepam* and *lorazepam are alternatives.*

C- Opioid analgesics: large doses of Opioid analgesics have been used in combination with large doses of benzodiazepines to achieve a general anesthetic state, particularly in

patients undergoing cardiac surgery or other major surgery when the patient s circulatory reserve is limited. Morphine, fentanyl, sufentanil have been used.

D- Ketamine: differing from most other intravenous anesthetics in that it produces significant analgesia. The characteristic state observed after an induction dose of ketamine is known as "dissociative anesthesia," where in the patient's eyes remain open with a slow nystagmic gaze (i.e. the patient may appear awake and reactive but does not respond to sensory stimuli). The term "***dissociative anesthesia,"*** is used to describe these qualities of profound analgesia, amnesia & superficial level of sleep. *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. *Ketamine* may be used illicitly, since it causes a dream-like state and hallucinations similar to *phencyclidine* (PCP).

E- Etomidate:

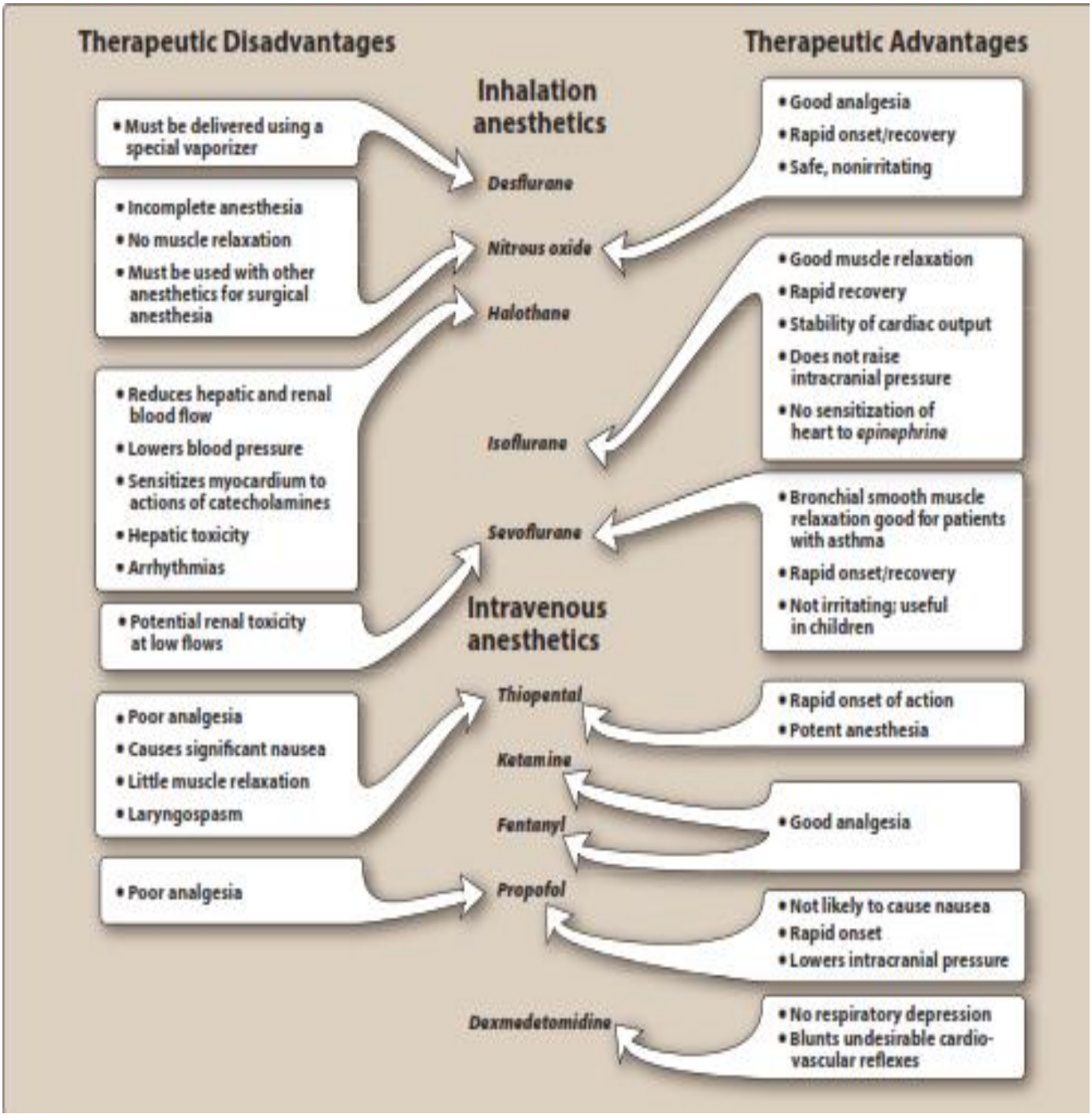
Is used to induce anesthesia, it is a hypnotic agent but lacks analgesic activity.

Induction is rapid, short acting .It is only used for patients with coronary artery disease or cardiovascular dysfunction, No effect on heart and circulation.

Adverse effects: a decrease in plasma cortisol and aldosterone levels which can persist for up to eight hours.

F- Propofol: Phenol derivative, it is an IV sedative-hypnotic used in the induction and or maintenance of anesthesia. Onset is smooth and rapid (40 seconds), It is occasionally accompanied by excitatory phenomena, such as muscle twitching, spontaneous movement, or hiccups. ((has similar effect of barbiturates but with rapid recovery, it has antiemetic effect, marked decrease in B.P lead to hypotension.

G- Dexmedetomidine : Dexmedetomidine is a sedative used 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.


Therapeutic Disadvantages
Therapeutic Advantages
Inhalation anesthetics
• Must be delivered using a special vaporizer
Desflurane
• Good analgesia
• Rapid onset/recovery
• Safe, nonirritating
• Incomplete anesthesia
• No muscle relaxation
• Must be used with other anesthetics for surgical anesthesia
Nitrous oxide
Halothane
• Good muscle relaxation
• Rapid recovery
• Stability of cardiac output
• Does not raise intracranial pressure
• No sensitization of heart to epinephrine
• Reduces hepatic and renal blood flow
• Lowers blood pressure
• Sensitizes myocardium to actions of catecholamines
• Hepatic toxicity
• Arrhythmias
Isoflurane
Sevoflurane
• Bronchial smooth muscle relaxation good for patients with asthma
• Rapid onset/recovery
• Not irritating; useful in children
• Potential renal toxicity at low flows
Intravenous anesthetics
Thiopental
• Rapid onset of action
• Potent anesthesia
• Poor analgesia
• Causes significant nausea
• Little muscle relaxation
• Laryngospasm
Ketamine
Fentanyl
• Good analgesia
• Poor analgesia
Propofol
• Not likely to cause nausea
• Rapid onset
• Lowers intracranial pressure
Dexmedetomidine
• No respiratory depression
• Blunts undesirable cardiovascular reflexes