General Anesthetics

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Definitions:

General anesthesia is intended to produce **5 desired effects**: (unconsciousness, amnesia, analgesia, skeletal muscle relaxation, and inhibition of autonomic reflexes). The purpose of these effects is **loss of response to surgical incision.**

It is difficult to obtain **these 5 desired effects** with a single drug because the concentration needed to achieve all these effects will be toxic. So, it is better to use more than one drug to achieve them without the need to increase the dose (balanced anesthesia).

Balanced anesthesia:
Is employing multiple drugs (IV anesthetics, inhaled anesthetics, sedative-hypnotics, opioids, neuromuscular blocking drugs) to minimize the adverse effects of using single anesthetic agent.

History:

The first reliable documentation of an operation to be performed under general anesthesia was conducted by the Japanese surgeon, **Hanaoka Seishu**, in 1804 who performed a partial mastectomy for breast cancer on a 60-year-old woman. He used an oral solution composed of blend of some herbal extracts to perform the anesthesia.

Phases of anesthesia:

1. Before surgery (preanesthetic medications):

One hour before operation, the patient is given **anxiolytic** to relieve anxiety and may be given **metoclopramide** to hasten gastric evacuation and prevent vomiting and aspiration pneumonia.

2. During surgery:

- Induction of anesthesia usually by an IV anesthetic
- Maintenance is achieved by inhalation anesthetic
- The patient is also given NMBs

3. After surgery:

- The patient is not left until respiration is normal
- Relieve of pain by an opioid

Classification of general anesthetics:

I. Inhalation agents:

- Volatile liquids: isoflurane – sevoflurane – desflurane – enflurane – halothane
- Gases: nitrous oxide – xenon

II. IV agents: Propofol **– t**hiopental – etomidate **–** ketamine – **m**idazolam

Pharmacodynamics:

I. Mechanism of general anesthesia:

(a) Old theory: lipid solubility (Meyer-Overton rule)

- States that anesthetic agents are highly lipid soluble and the anesthetic potency is correlated to the degree of lipid solubility.
- Because of this lipid solubility they dissolve in the neuronal cell membrane and affect membrane fluidity and the physical properties of cell membranes.

(b) Modern theories:

1. Activation of $GABA_A$ receptor:
- Most anesthetic agents directly and indirectly facilitate a GABA-mediated increase in chloride conductance to hyperpolarize and inhibit neuronal membrane activity.
- Examples: Propofol, etomidate, isoflurane, benzodiazepines (midazolam, lorazepam, diazepam), and barbiturates (e.g. sodium thiopental)

2. Blocking of NMDA receptor: Nitrous oxide and ketamine inhibit excitatory glutamate-gated ion channels (NMDA receptors).

3. Opening of two-pore potassium channels (K_{2P}):
- Opening of these channels causes neuronal hyperpolarization which reduces neuronal excitability.
- Examples: halogenated inhalation anesthetics

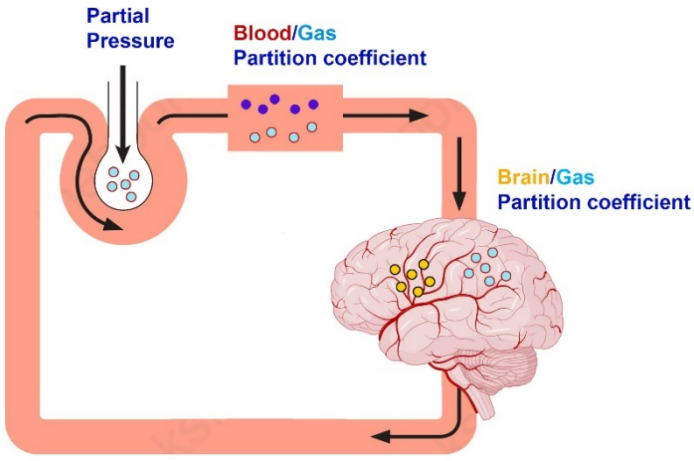
II. Stages of general anesthesia based on Guedel's classification (1937):
This classification was designed based on the use of a single inhalational anesthetic (diethyl ether). Now, because of the use of intravenous induction agents with muscle relaxants, and the discontinuation of ether, elements of Guedel's classification have become **out of date**. Modern techniques ensures smooth induction, maintenance, and recovery without passing through these stages.

Stage I - Analgesia	Stage II – Excitement	Stage III – Surgical anesthesia	Stage IV - Medullary depression
The receiver of the anesthesia primarily feels analgesia followed by amnesia.	- Severe confusion and amnesia. - Irregular respiration. - Nausea and vomiting. - Struggling and panic.	- Regular respiration. - Regular HR. - Loss of eye and ms reflexes. - Normal BP	- Depression of RC. - Circulatory collapse due to ↓↓ of VMC. - Fully dilated pupil - Coma and death

I. INHALED ANESTHETICS

1. Volatile liquids: isoflurane – sevoflurane – desflurane – enflurane – halothane
2. Gases: nitrous oxide – xenon

Pharmacokinetics of inhaled anesthetics:



- Diffusion of the anesthetic gas from the lung alveoli to blood depends on:
  - **The partial pressure** between the alveoli (air) and blood: A high partial pressure drive more drug into blood and produce **more** anesthetic effect.
  - **The partition coefficient: it** is the relative solubility of a gaseous drug in different tissues. High blood:gas partition coefficient means more solubility in blood compared to air → more plasma protein binding → **slow** induction and **slow** recovery. High brain:gas partition coefficient means more solubility in brain tissue → **rapid** induction.
  - **Cardiac output (COP):** induction of anesthesia is **proportionally** related to cerebral blood flow and **inversely** related to pulmonary blood flow (PBF).

- Inhaled anesthetics are eliminated via **expiration**. This process depends on the anesthetic blood:gas partition coefficient, tissue solubility, PBF, and patient respiratory rate.
- **Metabolism** of inhaled anesthetics is **not** a major route of drug elimination
- **The minimum alveolar concentration (MAC):** is the concentration of an inhalation agent in the alveoli that produce loss of response to surgical incision in 50% of subjects.
  - The lower the MAC value, the more **potent** the agent.
  - Increasing age, pregnancy, hypothermia, and hypotension will decrease MAC.
  - MAC is independent of gender and weight

Adverse effects of inhaled anesthetics:

1. Malignant hyperthermia:
- Is a rare (1:20000), but life-threatening condition that may occur when anesthetics are used with NMBs like succinylcholine.
- It is due to genetic abnormality in Ca2+ release channels **(ryanodine receptor)** in sarcoplasmic reticulum (SR) of muscle cells, leading to massive release of Ca+2 from SR following exposure to inhaled anesthetics or succinylcholine.
- Symptoms include muscle spasm, hyperthermia, hypertension, tachycardia, and hyperkalemia.
- Treatment includes **dantrolene**, a muscle relaxant that blocks Ca2+ release channels + supportive measures.

2. CNS: Rise of IC pressure due to VD of cerebral blood vessels.

3. CVS:
- **Hypotension:** due to myocardial depression and peripheral VD.
- **Cardiac arrhythmia:** especially with **halothane**.

4. Respiratory:
- **Desflurane** is a pulmonary irritant and can cause **bronchospasm**.
- Inhibition of mucociliary function.

5. Liver: Halothane can cause acute liver injury ***(halothane hepatitis)***.

6. Uterus: Inhaled anesthetics cause **uterine relaxation** which can be helpful when uterine relaxation is required for intrauterine fetal manipulation or manual extraction of a retained placenta. However, it can also lead to **increased uterine bleeding** after delivery when uterine contraction is desired.

II. INTRAVENOUS ANESTHETICS

Propofol – thiopental – etomidate – ketamine – midazolam

- They are commonly used for rapid induction of anesthesia.
- IV anesthetics are **highly lipophilic** drugs, upon administration, they rapidly **distribute** in the highly vascular tissues including the brain causing rapid **induction** of anesthesia. Termination of anesthesia is due to **redistribution** of the drug from nervous tissue to other tissues such as muscles, viscera, and adipose tissue.
- Prolonged administration can lead to saturation of adipose tissue and slowing of the redistribution phase → prolongation of anesthesia.

Propofol (Diprivan 1%)

- The most commonly used IV agent for induction of anesthesia.

- Propofol can be also used by **continuous IV infusion** to maintain anesthesia (total intravenous anesthesia, TIVA).
- It is administered as an oil-in-water emulsion which can cause **pain** at the injection site. **Fospropofol** is a water-soluble derivative that is less painful and rapidly converted to propofol in the body.
- **Adverse effects:**
  - Pain at the site of injection
  - **Propofol infusion syndrome** occurs with prolonged infusion and consists of severe metabolic acidosis, skeletal muscle necrosis (rhabdomyolysis), hyperkalaemia, lipaemia, hepatomegaly, renal failure, arrhythmia and cardiovascular collapse.

Thiopental

- Thiopental is the only remaining barbiturate in common use.
- Used **only for induction** of anesthesia (not for maintenance).
- It is highly **lipophilic** drug. On IV injection, thiopental causes unconsciousness within about 20 s, lasting for 5–15 min before it **redistributes** to fatty tissues.
- **Adverse effects:**
  - High dose can cause hypotension, RC depression, and myocardial **depression**.
  - The solution of thiopental is **highly alkaline**, if injected SC or IM, it causes local **tissue necrosis** and ulceration that can result in gangrene.
  - Like other barbiturates, it is hepatic microsomal **enzyme inducer**.

Etomidate

- Etomidate is very similar to thiopental but it is more rapidly metabolized, **less hypotensive** and less myocardial depressant.
- **Adverse effects:**
  - Etomidate suppresses the production of **adrenal steroids**, an effect that has been associated with an increase in mortality in severely ill patients (patient with **sepsis**).
  - Postoperative **nausea and vomiting**.

Ketamine (Ketalar)

- The characteristic state observed after an induction dose of ketamine is known as **"dissociative anesthesia,"** wherein the patient's eyes remain open with a slow nystagmic gaze.
- Ketamine's mechanism of action includes inhibition of the NMDA receptor.
- It differs from most other IV anesthetics in:
  - It produces significant **analgesia**
  - It **raises** the blood pressure
  - Does **not** affect respiration.
- The adverse effects are **less marked in children** making it preferred in pediatrics.
- **Adverse effects:**
  - Increase IC tension
  - Hallucinations and psychiatric disturbances on recovery.

Midazolam (Dormicum)

- It is a very short acting BZ. It has **rapid** onset and **short** duration.
- May be used **preoperatively** for sedation and to reduce anxiety.
- It is used as a sole agent for surgical and **diagnostic procedures** that do not require analgesia (endoscopy, cardiac catheterization).
- The actions of the BZs can be reversed with **flumazenil.**