In this article, we will study in detail about the phases of anesthesia, classification, mechanism of action, and adverse effects/toxicity of general anesthetics. Important therapeutic aspects of individual drugs will also be studied.

Definition of General Anesthesia

General anesthesia is a reversible state characterized by **loss of reception and perception of stimuli**. Important effects seen in general anesthesia are **sedation**, **reduced anxiety**, lack of awareness and amnesia, **skeletal muscle relaxation**, suppression of undesirable reflexes and **analgesia**.

General anesthesia is used for performing **complex surgeries**.
Classification of General Anaesthetics

Inhalational anesthetics:

- **Gas**: nitrous oxide
- **Liquids**: ether, halothane, enflurane, isoflurane, desflurane, sevoflurane

Intravenous Anesthetics:

- **Inducing agents**: thiopentone sodium, methohexital sodium, propofol, etomidate
- **Slower acting drugs**:
  - Benzodiazepines: diazepam, lorazepam, midazolam
  - Dissociative anesthesia: ketamine
  - Opioid Analgesia: fentanyl

Characteristics of Ideal General Anesthetics

- Rapid onset of action
- Should not cause irritation and vomiting
- Should provide adequate immobility, analgesia and muscle relaxation
- Minimal adverse effects on liver, heart and other organs
- Cheap and stable
- Low blood solubility
- Should have high potency (low MAC)

Phases of General Anesthesia

Anesthesia is characterized by three phases:

1. **Induction phase**: This is from the time of administration of anesthetic to the development of effective anesthesia. Induction of anesthesia with intravenous agent (e.g. propofol) will produce unconsciousness in 30 seconds. For achieving
depth of anesthesia, some drugs are added to the anesthetics either by inhalation or intravenous routes. For example, **neuromuscular blockers** like succinylcholine and rocuronium are administered to achieve sufficient muscle relaxation and facilitate tracheal intubation. **Important:** Propofol is the most commonly used i.v. induction agent as it is less **sedative** and **nauseatic** than the other induction agents, especially barbiturates.

2. **Maintenance phase:** It includes providing sustained anesthesia. After the administration of the anaesthetic agent, the vital signs and response to stimuli are continuously monitored to balance the amount of drug inhaled, or infused, with the depth of anesthesia. Sevoflurane (also used for induction), desflurane and nitrous oxide are commonly used agents used for the maintenance of anesthesia.

3. **Recovery phase:** This is the time from the discontinuation of anesthetic until consciousness and reflexes return. It is the reverse of the induction phase. The patient is monitored until there is a return of normal physiologic functions.

**Summary**

1. Pre-operative assessment of the patient
2. Evaluation of the airway
3. Induction of general anesthesia
4. Securing the airway
5. Maintenance of general anesthesia
6. Reversal of muscle relaxation (if necessary)
7. Recovery from general anesthesia
8. Management of pain
9. Recovery room care

**Depth of Anesthesia**

The process of achievement of effective anesthesia is dependent on the depth of anesthesia. It includes four stages:

**Stage 1: Analgesia**

In this stage, awareness of pain is decreased because of interference of sensory transmission with spinothalamic tract. The condition progresses from conscious to conversational to **drowsy**. Consciousness is impaired, but not lost.

**Stage 2: Disinhibition**

The patient is in a state of delirium and excitation. The patient may shout or struggle in this stage. Vomiting, involuntary defecation or micturition may also occur. The operation should not be conducted during this stage.

**Stage 3: Surgical anesthesia**
It is characterized by the following activities:

- Roving eyeballs movements
- Loss of corneal and laryngeal reflexes
- Pupil dilation
- Intercostal paralysis
- Patient is unconscious in this stage.

**Stage 4: Medullary depression**

Severe respiratory and cardiovascular depression results in this stage. It requires mechanical and pharmacological support to prevent the death of a patient.

**Mechanism of Action of General Anesthetics**

General anesthetics act either by inhibiting the excitatory receptors (NMDA) or facilitating the actions of inhibitory receptors (GABA). Mechanism of action of general anesthetics is best explained by Meyer-Overton lipid solubility theory. This theory put forth the following hypothesis:

The greater the lipid solubility of an anesthetic agent, the higher will be its potency. This theory is quite old, but it still has significance and relevance in modern medicine to explain the correlation of lipophilicity of anesthetics and their potency.

Also, anesthetic agents don’t specifically act at one single ion channel, but they may act on two or more types of ion channels.

Barbiturates, benzodiazepines, etomidate and propofol and all inhaled anesthetics act by facilitating the actions of inhibitory receptors, GABA. Ketamine and nitrous oxide act by inhibiting the N-methyl-Daspartate (NMDA) receptor.

**Inhalational Anesthetics**

Inhalational anesthetics are commonly used as an induction and maintenance agent. The speed of induction of anesthetic effects depends on factors like:

- **Solubility**: the greater the solubility, the greater will be the induction of an anesthetic.
- **Inspired gas partial pressure**: a higher partial pressure of the gas in the lungs results in the greater speed of induction of an anesthetic.
- **Ventilation rate**: the greater the ventilation rate, the faster is the effect of an anesthetic agent.
- **Pulmonary blood flow**: a high pulmonary blood flow results in the slow onset of the effect of an anesthetic.
- **Arteriovenous concentration gradient**: the greater the arteriovenous concentration gradient, the slower will be the induction.

### Elimination of Inhalational Anesthetics

All the inhalational anesthetics are excreted from the lungs. Due to the high lipid solubility of general anesthetics, they persist in the adipose tissue for longer periods. Halothane and methoxyflurane are metabolized by liver enzymes. Due to the high amount of **hepatic metabolism** of halothane, it shows the highest cases of hepatic injuries among all the inhalational anesthetics.

### Minimum Alveolar Concentration (MAC)

The potency of inhaled anesthetics is measured by the minimum alveolar anesthetic concentration (MAC), defined as the alveolar concentration required to prevent the response to a standardized painful stimulus in 50% of subjects.

**Always remember**: MAC is a measure of potency only applicable for inhalational anesthetics.

The MAC value of inhaled anesthetics is somewhat related to its lipid solubility. The higher the lipid solubility, the higher will be its potency and the lower will be the MAC value. The MAC value for halothane is 0.75% (high potency) and the MAC value of nitrous oxide is 104% (low potency).

### Effects of Inhaled Anesthetics on Organ Systems

#### CNS Effects

Anesthetics decrease the **global cerebral metabolic rate**. This is thought to be the mechanism behind the unconsciousness produced by general anesthetics. They act by **reducing the vascular resistance in the brain**, in turn, causing an increase in cerebral blood flow leading to an increase in intracranial pressure.

**Enflurane**, given in high doses, may cause spike-and-wave activity and muscle twitching. Because of low blood gas partition coefficient, nitrous oxide has a low anesthetic potency. (High MAC) nitrous oxide exerts analgesic and amnestic actions.

#### Cardiovascular Effects

A moderate decrease in arterial blood pressure is seen when the drug is given by inhalation route. Halothane and enflurane decrease **cardiac output**; isoflurane, desflurane and sevoflurane cause **peripheral vasodilatation**.

Inhaled anesthetics depress **myocardial function** - nitrous oxide exerts the least effects on the myocardium. Halothane also causes depression of **myocardial contractibility** and can cause **arrhythmia**.

#### Respiratory Effects

Most of the inhaled anesthetics produce **bronchodilation** except desflurane, which produces **bronchospasm**. They also increase respiratory rate, decrease tidal volume and minute ventilation.
Halothane

Due to hepatotoxicity, its use is nearly eliminated in North America. It also causes myocardial depression. Halothane is metabolized to 20-30% in the liver, as compared to newer inhalational anesthetics, enflurane (2%), sevoflurane (1%), isoflurane and desflurane (less than 0.2%).

Isoflurane

It is the most potent anesthetic among the inhalational anesthetics. It has rapid (7-10 min) and short duration of action.

Desflurane

It is not used as an induction anesthetic as it causes air way irritation (cough, laryngospasm and salivation). It also causes bronchospasm.

Sevoflurane

It is one of the most frequently and commonly used inhalational anesthetics for the induction of anesthesia. It produces a rapid onset of action (within a minute). Also, it is a preferred anesthetic as it has very less reported cases of hepatotoxicity.

Other advantages of sevoflurane are a lack of pungency, odor and bronchospasm.

Nitrous Oxide

It is never used alone as an anesthetic agent, but it is used as adjunct with a potent inhalational agent. It produces postoperative vomiting and nausea. Also, it is important to note that nitrous oxide causes inactivation of vitamin B12 – it can cause neurodegeneration in vitamin B12 deficient patients.

It produces poor muscle relaxation, but a rapid induction of anesthesia. It is less potent (high MAC: 104%).

Toxicity of Inhaled Anesthetics
In patients with **hypovolemic shock**, halothane causes **postoperative hepatitis**. **Megaloblastic anemia** may occur because of the decrease in methionine synthesis with increased exposure to nitrous oxide.

Mutation in gene loci corresponding to **ryanodine receptor (RyR1)** results in an uncontrolled release of calcium by **sarcoplasmic reticulum** of skeletal muscle, leading to muscle spasm, hyperthermia and autonomic lability because of the simultaneous use of neuromuscular blockers (especially **succinylcholine**) and anesthetics. This condition is called **malignant hyperthermia**, which is life threatening. **Dantrolene**, along with supportive management, is used in the treatment of this condition.

**Warning in pregnancy**: Transient use of **nitrous oxide** may cause **aplastic anemia** in the fetus. **Oral clefts** have occurred in fetuses when mothers received **benzodiazepines** in early pregnancy. Benzodiazepines should not be used during labor because of resultant **temporary hypotonia** and altered thermoregulation in the newborn.

**Intravenous Anesthetics**

**Barbiturates**

**Thiopental** is an ultrashort-acting barbiturate with high lipid solubility. It acts by blocking **GABAa receptors**. The high lipid solubility of thiopental and methohexital helps in fast entry into the brain and results in surgical anesthesia in circulation time (<1 min).

These drugs are used for the induction of anesthesia and for short surgical procedures. Termination of anesthetic effects of thiopental is by redistribution from brain to highly perfused tissues and elimination is by **hepatic metabolism**.

Barbiturates depress **cerebral blood flow** and cause a **decrease in intracranial pressure**, and also act as **respiratory and circulatory depressants**.
Benzodiazepines

Anesthetics are never used alone, but always used in **adjunct** with other anesthetics. Midazolam is used adjunctively with inhaled anesthetics and intravenous opioids. It is preferred over diazepam. It has a rapid and short duration of action; it causes severe **postoperative respiratory depression**.

Ketamine

Ketamine produces **dissociative anesthesia** characterized by analgesia, amnesia, and feeling of dissociation from the body. It acts by blocking **NMDA receptors**. It is a cardiac stimulant (increase BP, heart rate, cardiac output) and increases intracranial pressure.

Ketamine is contraindicated in **glaucoma** or **acute globe injury**. It is metabolised primarily through the liver and excreted mostly in urine. It is a suitable **anesthetic for small operations (consciousness is not lost)**.

Opioids

Morphine and fentanyl are used with other CNS depressants (nitrous oxide, benzodiazepines) and can be used in patients who cannot tolerate full general anesthesia.

Opioids, when given intravenously, will cause chest wall rigidity, impairing ventilation and causing **respiratory depression**, which is reversed postoperatively with naloxone. The route of administration can be intravenously, epidurally, or intrathecally (into the cerebrospinal fluid).

It has a short duration of action (30-50 min).

**Neuroleptanesthesia** is a state of analgesia and amnesia, produced when fentanyl is used with droperidol and nitrous oxide.

Newer opioids like alfentanil and remifentanil have been used for the induction of anesthesia.
Propofol

Propofol produces anesthesia (in 15-45 seconds) as rapidly as the intravenous barbiturates, and recover more rapidly. It has agonistic actions on GABAa receptors. It has antiemetic actions, and recovery is not delayed after prolonged infusion.

This is the anesthetic of choice in outpatient surgery and for producing prolonged sedation for patients admitted in critical care settings. Propofol decreases peripheral resistance and thus causes hypotension (in 15.7% patients) during induction.

Etomidate

This drug causes fast induction with very little change in cardiac function or respiratory rate and has a short duration of action of anesthesia and lacks analgesic properties. The primary advantage is in anesthesia for patients with limited cardiac or respiratory reserve.

Etomidate on injection causes pain and myoclonus. It also causes nausea postoperatively. Adrenal suppression (inhibits cortisol) is seen on administration for a long period.

Review Questions on General Anesthesia

The correct answers can be found below the references.

1. Which of the following inhalational anesthetics shows the highest rate of hepatitis?
   1. Halothane
   2. Isoflurane
   3. Desflurane
   4. Sevoflurane
   5. Nitrous oxide

2. Which of the following inhalational anesthetics causes bronchospasm?
   1. Halothane
   2. Isoflurane
   3. Desflurane
   4. Sevoflurane
   5. Nitrous oxide

3. The mechanism of action of ketamine is?
   1. Blockage of NMDA receptors
   2. Blockage of GABAa receptors
   3. Blockage of GABAb receptors
   4. Blockage of opioids receptors
   5. Blockage of calcium channels

References


Howland RD, Mycek MJ, Harvey RA, Champe PC. Lippincott's illustrated reviews:


Overview of anesthesia and anesthetic choices via uptodate.com


Anaesthesia and intensive care medicine via anaesthesiajournal.co.uk


Isoflurane via medscape.com

Halothane hepatitis via uptodate.com General anesthesia: Induction via uptodate.com


Correct answers: 1A, 2C, 3A

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