Definition

Anesthesia refers to the abolition of sensation. 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 protective reflexes, and analgesia. The most important of these factors are analgesia, amnesia, and skeletal muscle relaxation. They are referred to as the “triad” of anesthesia and must be achieved during the administration of any anesthetic agent.

General anesthesia is used for performing complex surgeries.
Types

There are 3 main categories of general anesthetics.

**Inhalational:**
- **Gas:** Nitrous oxide
- **Liquids:** Ether, halothane, enflurane, isoflurane, desflurane, sevoflurane

**Intravenous:**

**Inducing agents:** Thiopentone sodium, methohexital sodium, propofol, etomidate

**Slower-acting:**
- **Benzodiazepines:** Diazepam, lorazepam, midazolam
- **Dissociative:** Ketamine (see image)
- **Opioid analgesia:** Fentanyl

**Characteristics**

The best general anesthetics have the following characteristics:

- Rapid onset of action due to a low blood/gas solubility
- **Pleasant odor and non-irritating to the respiratory tract**
- Provide adequate immobility, analgesia, and muscle relaxation
- Minimal adverse effects on the liver, heart, and other organs
- Cheap and stable so that they do not react with parts of the anesthetic circuit
- Achieve the triad of anesthesia
- High potency (low minimum alveolar anesthetic [MAC]).

An ideal anesthetic agent that can achieve all desired effects in all populations does not yet exist. Therefore, the best agent needs to be chosen from the available choices through weighing the pros and cons of each.
Phases

Anesthesia is characterized by 3 phases:

**Induction phase:** This phase comprises the time of administration of an anesthetic to the development of effective anesthesia. Induction of anesthesia with an intravenous agent (eg, propofol) will produce unconsciousness in 30 seconds. To achieve the needed depth of anesthesia, some drugs are added to the anesthetics either by inhalation or intravenous routes. For example, neuromuscular blockers such as succinylcholine and rocuronium are administered to achieve sufficient muscle relaxation and facilitate tracheal intubation (see image).

![Intubating the patient. A. The neck is too flexed. B. The axis from brow to chest wall should be a straight line for ideal intubating conditions. C. The neck is too extended. Image created by Lecturio](image)

Propofol is the most commonly used IV induction agent as it is less sedative and less likely to induce nausea than the other induction agents, especially barbiturates.

**Maintenance phase:** This phase includes providing sustained anesthesia. After the administration of the anesthetic 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 for the maintenance of anesthesia.

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

**Summary of the Process**

1. Preoperative assessment of the patient
2. Evaluation of the airway
3. Induction of general anesthesia
4. Securing of 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**

Achieving effective anesthesia depends on the depth of anesthesia. It includes 4 stages.

**Stage 1: Analgesia**

In this stage, awareness of pain is decreased because of the interference of sensory
transmission with the spinothalamic tract. The patient’s 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. They may shout or struggle at this stage. Vomiting, involuntary defecation, or micturition may also occur. The operation should not be conducted during this stage.

**Stage 3: Surgical Anesthesia**

Surgical anesthesia is characterized by the following activities:

- Roving-eye movements
- Loss of corneal and laryngeal reflexes
- Pupil dilation
- Intercostal paralysis
- Unconsciousness

**Stage 4: Medullary Depression**

Severe respiratory and cardiovascular depression occurs in this stage. This state requires mechanical ventilation and pharmacological support to prevent the patient’s death.

**Mechanism of Action**

General anesthetics act either by inhibiting the excitatory receptors (N-methyl-D-aspartate [NMDA]) or facilitating the actions of inhibitory receptors (gamma-aminobutyric acid [GABA]). The mechanism of action of general anesthetics is best explained by the Meyer-Overton lipid solubility theory, which posits that the greater the lipid solubility of an anesthetic agent, the higher its potency. Although this theory is quite old, it still adequately explains the correlation of lipophilicity of anesthetics and their potency.

As well, anesthetic agents do not specifically act on a single ion channel; instead, they may act on 2 or more types.

Barbiturates, benzodiazepines, etomidate, propofol, and all inhaled anesthetics act by facilitating the actions of inhibitory receptors, GABA. The potentiation of GABA receptors leads to opening of the chloride ion channels, which later hyperpolarize or short circuit the synaptic membrane.
**Ketamine** and nitrous oxide act by inhibiting the **NNMDA receptor**. Ketamine is a noncompetitive antagonist of the NMDA receptor Ca²⁺ channel pore and inhibits NMDA receptor activity by interacting with phencyclidine.

**Inhalational Anesthetics**

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

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

**Elimination of Inhalational Anesthetics**

All 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 produces the highest number of hepatic injuries among all the inhalational anesthetics.

**Minimum Alveolar Concentration**

The potency of inhaled anesthetics is measured by the MAC, which is defined as the least amount of alveolar concentration of an anesthetic agent at 1 atmosphere required to prevent the response to a standardized painful stimulus in 50% of subjects. MAC is a measure of potency that only applies to inhalational anesthetics.

The MAC value of inhaled anesthetics is somewhat related to its lipid solubility. The higher the lipid solubility, the higher its potency and the lower the MAC value. The MAC value for halothane is 0.75% (high potency); for isoflurane, it is 1.15%; sevoflurane, 1.71%–2.05%; and nitrous oxide, 104% (low potency).

**Effects of Inhaled Anesthetics on Organ Systems**

**Central Nervous System Effects**

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

**Enflurane**, given in high doses, may cause spike-and-wave activity and muscle twitching. Because of the low blood gas partition coefficient, nitrous oxide has a low anesthetic potency. 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 fewest effects on the myocardium. Halothane also causes depression of myocardial contractibility and arrhythmia.

Isoflurane causes coronary vasodilation, which, in the presence of fixed coronary stenotic lesions, can cause a redistribution of coronary blood supply from the endocardium to the epicardium, a state known as coronary steel effect.

**Respiratory Effects**

Most inhaled anesthetics (except desflurane) produce bronchodilation, which produces bronchospasm. They also increase respiratory rate and decrease tidal volume and minute ventilation (ie, they are respiratory depressants).

Isoflurane and desflurane induce respiratory tract irritation and therefore may cause coughing, breath holding, and increased bronchial secretions.

**Halothane**

Due to hepatotoxicity, halothane is rarely used in North America. It also causes myocardial depression. Halothane is metabolized to 20%-30% in the liver compared with newer inhalational anesthetics such as enflurane (2%), sevoflurane (1%), isoflurane, and desflurane (< 0.2%).

**Isoflurane**

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

**Desflurane**

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

**Sevoflurane**

Sevoflurane is one of the most frequently and commonly used inhalational anesthetics for the induction of anesthesia. It produces rapid onset of action (within 1 minute). It is also a preferred anesthetic, as it has a much lower incidence of hepatotoxicity. Other advantages include a lack of pungency, odor, and bronchospasm.

**Overview of Commonly Used Inhaled Anesthetics**

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<th>Isoflurane</th>
<th>Desflurane</th>
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Nitrous Oxide

Common adverse effects of nitrous oxide include the following:

- **Postoperative vomiting and nausea**
- **Inactivation of vitamin B12**. Nitrous oxide can cause neurodegeneration in vitamin B₁₂-deficient patients that may lead to peripheral neuropathy with protracted use.
- **Poor muscle relaxation**, but a rapid induction of anesthesia, as it is less potent (MAC = 104%).
- Fink effect/diffusion hypoxia

Toxicity of Inhaled Anesthetics

1. **Hepatotoxicity**

   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 (see image).

2. Malignant hyperthermia

Mutation in gene loci corresponding to the ryanodine receptor (RyR1 gene) results in an uncontrolled release of calcium by a 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 and is life-threatening. Dantrolene, along with supportive management, is used to treat this condition.

3. Teratogenicity

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 GABA<sub>A</sub> receptors. The high lipid solubility of thiopental and methohexital aids its 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 the brain to highly perfused tissues, and elimination is by hepatic metabolism.

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

Common adverse effects include:

- Anaphylactic reactions
- Tissue necrosis with extravasation
- Induction of arterial constriction and thrombi formation

Benzodiazepines

These anesthetics are never used alone but always in adjunct with other anesthetics. Midazolam is used adjunctively with inhaled anesthetics and intravenous opioids. Thus, it is commonly used for procedures such as endoscopy in intensive care units. Midazolam is preferred over diazepam as it has a rapid and short duration of action with a safer adverse effect profile. These anesthetics cause severe postoperative respiratory depression.

The clinical effects of benzodiazepines can be reversed with flumazenil.

Ketamine
Ketamine produces **dissociative anesthesia** characterized by analgesia, amnesia, and a feeling of dissociation from the body. The patient experiences deliriums, unpleasant dreams, and hallucinations. It acts by blocking **NMDA receptors**. It is a cardiac stimulant (increases blood pressure, heart rate, and cardiac output) and increases intracranial pressure.

Ketamine is contraindicated in **glaucoma** or **acute globe injury** (see image). It is metabolized primarily through the liver and excreted mostly in urine. It is a suitable **anesthetic for small operations, as consciousness is not lost. However, it is associated with pain on injection and therefore may necessitate co-administration with a local anesthetic agent.**

**Opioids**

Morphine and fentanyl are used with other central nervous system 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 such alfentanil and remifentanil have been used for the induction of anesthesia.

**Propofol**

Propofol produces anesthesia (in 15–45 seconds) as rapidly as intravenous barbiturates, but patients recover faster. It has **agonistic actions on GABA receptors**. It also has **antiemetic actions**, and recovery is not delayed after prolonged infusion.

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

**Etomidate**

This drug causes fast induction with very little change in cardiac function or respiratory rate, has a short duration of action, and lacks analgesic properties. The primary advantage is in 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 over a long period of time.

**References**


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**Anaesthesia and intensive care medicine** via anaesthesiajournal.co.uk


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