

Anesthetics 1

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Anesthetics are agents that bring about reversible loss of sensation and consciousness. They are divided into two main groups: general anesthetics and local anesthetics. Drugs are chosen to provide safe and efficient sedation based on the type and duration of the procedure and patient characteristics, such as organ function, medical conditions, and concurrent medications.

Preoperative medications provide anxiolysis and analgesia, and mitigate unwanted side effects of the anesthetic or the procedure itself. Neuromuscular blockers enable endotracheal intubation and muscle relaxation to facilitate surgery. Potent general anesthetic medications are delivered via inhalation and/or intravenously. Except for *nitrous oxide*, inhaled anesthetics are volatile, halogenated hydrocarbons, while intravenous (IV) anesthetics consist of several chemically unrelated drug classes commonly used to rapidly induce and/ or maintain a state of general anesthesia.

	TYPES OF GENERAL ANESTHETICS	
Inhalational anesthetics	Gas	Liquids
	Nitrous oxide	<i>Halothane</i> <i>Methoxyflurane</i> <i>Enflurane</i> <i>Isoflurane</i> <i>Desoflurane</i>
Intravenous anesthetics	Barbiturates: <i>Thiopentone</i> <i>Methohexitone</i> Nonbarbiturates: <i>Propofol</i> <i>Etomidate</i> Benzodiazepines: <i>Diazepam</i> <i>Lorazepam</i> <i>Midazolam</i>	
Dissociative anesthetics	<i>Ketamine</i>	

PATIENT FACTORS IN SELECTION OF ANESTHESIA

Drugs are chosen to provide safe and efficient anesthesia based on the type of procedure and patient characteristics such as organ function, medical conditions, and concurrent medications.

A. Status of organ systems

1. Cardiovascular system: Anesthetic agents suppress cardiovascular function to varying degrees. This is an important consideration in patients with coronary artery disease, heart failure, dysrhythmias, valvular disease, and other cardiovascular disorders. Hypotension may develop during anesthesia, resulting in reduced perfusion pressure and ischemic injury to tissues. Treatment with vasoactive agents may be necessary. Some anesthetics, such as *halothane*, sensitize the heart to arrhythmogenic effects of sympathomimetic agents.

Respiratory system: Respiratory function must be considered for all anesthetics. Asthma and ventilation or perfusion abnormalities complicate control of inhalation anesthetics. Inhaled agents depress respiration but also act as bronchodilators. IV anesthetics and opioids suppress respiration. These effects may influence the ability to provide adequate ventilation and oxygenation during and after surgery.

Liver and kidney: The liver and kidneys influence long-term distribution and clearance of drugs and are also target organs for toxic effects. Release of fluoride, bromide, and other metabolites of halogenated hydrocarbons can affect these organs, especially if they accumulate with frequently repeated administration of anesthetics.

Nervous system: The presence of neurologic disorders (for example, epilepsy, myasthenia gravis, neuromuscular disease, compromised cerebral circulation) influences the selection of anesthetic.

Pregnancy: Special precautions should be observed when anesthetics and adjunctive agents are administered during pregnancy. Effects of fetal organogenesis are a major concern in early 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 new born

B. Concomitant use of drugs

1. Multiple adjunct agents: 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; nonopioids (*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 in to 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.

LEVELS OF SEDATION

	MINIMAL (ANXIOLYSIS)	MODERATE	DEEP	GENERAL
Mentation	Responds normally to verbal stimuli	Responds purposefully to verbal or tactile stimuli	Responds purposefully to repeated verbal or painful stimuli	Unarousable to painful stimuli
Airway competency	Unaffected	Adequate	Intervention may be required	Intervention usually required
Respiratory system	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular system	Unaffected	Usually maintained	Usually maintained	May be impaired

STAGES OF GENERAL ANESTHESIA

General anesthesia is a reversible state of central nervous system (CNS) depression, causing loss of response to and perception of stimuli. The state of general anesthesia can be divided into three stages: induction, maintenance, and recovery. Induction is the time from administration of a potent anesthetic to development of unconsciousness, while maintenance is the sustained period of general anesthesia. Recovery starts with the discontinuation of the anesthetic and continues until the return of consciousness and protective reflexes. Induction of anesthesia depends on how fast effective concentrations of anesthetic reach the brain. Recovery is essentially the reverse of induction and depends on how fast the anesthetic diffuses from the brain. The depth of general anesthesia is the degree to which the CNS is depressed, as evident in electroencephalograms.

A. Induction

General anesthesia in adults is normally induced with an IV agent such as *propofol*, producing unconsciousness in 30 to 40 seconds. Often an IV neuromuscular blocker such as *rocuronium*, *vecuronium*, or *succinylcholine* is administered to facilitate endotracheal intubation by eliciting muscle relaxation. For children without IV access, nonpungent volatile agents, such as *sevoflurane*, are administered via inhalation to induce general anesthesia.

B. Maintenance of anesthesia

After administering the induction drug, vital signs and response to stimuli are vigilantly monitored to balance the amount of drug continuously inhaled or infused to maintain general anesthesia. Maintenance is commonly provided with volatile anesthetics, although total intravenous anesthesia (TIVA) with drugs such as *propofol* can be used to maintain general anesthesia. Opioids such as *fentanyl* are used for analgesia along with inhalation agents, because the latter alter consciousness but not perception of pain.

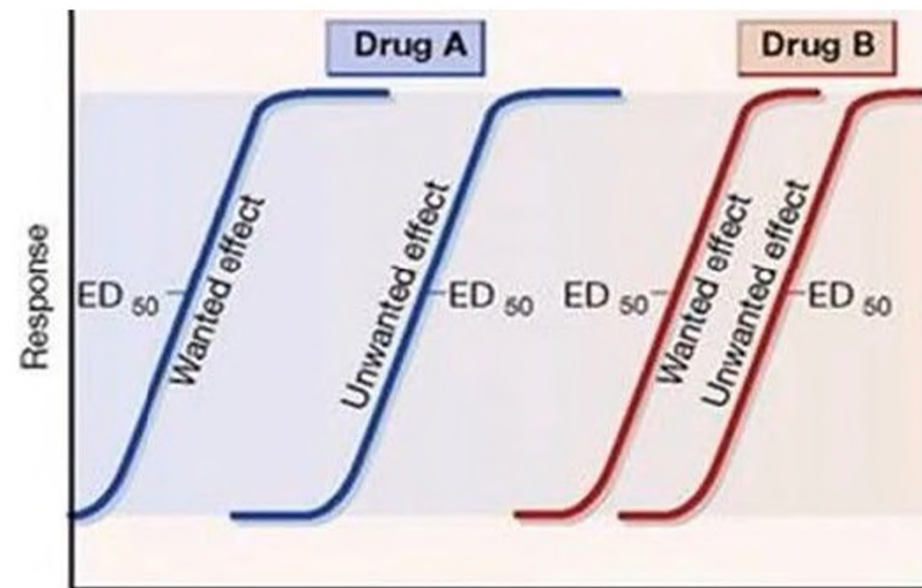
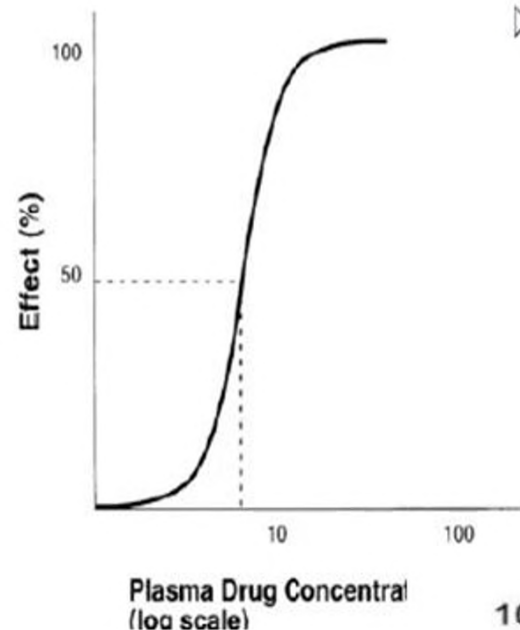
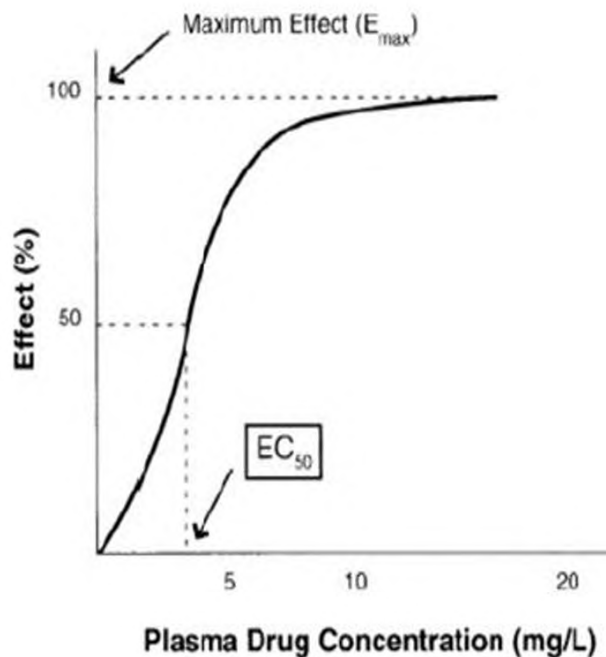
C. Recovery

After cessation of the maintenance anesthetic drug, the patient is evaluated for return of consciousness. For most anesthetic agents, redistribution from the site of action (rather than metabolism of the drug) underlies recovery. Neuromuscular blocking drugs are typically reversed after completion of surgery, unless enough time has elapsed for their metabolism. The patient is monitored to assure full recovery of all normal physiologic functions (spontaneous respiration, blood pressure, heart rate, and all protective reflexes).

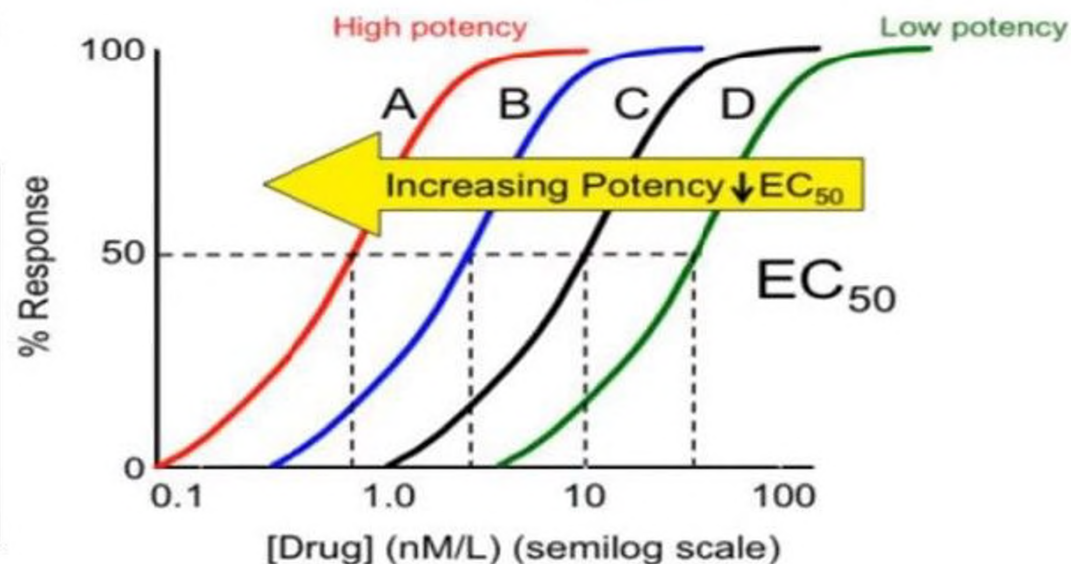
Depth of anesthesia

The depth of anesthesia has four sequential stages characterized by increasing CNS depression as the anesthetic accumulates in the brain . [Note: These stages were defined for the original anesthetic *ether*, which produces a slow onset of anesthesia. With modern anesthetics, the stages merge because of the rapid onset of stage III.]

1. Stage I—Analgesia: Loss of pain sensation results from interference with sensory transmission in the spinothalamic tract. The patient progresses from conscious and conversational to drowsy. Amnesia and reduced awareness of pain occur as stage II is approached.
2. Stage II—Excitement: The patient displays delirium and possibly combative behavior. A rise and irregularity in blood pressure and respiration occur, as well as a risk of laryngospasm. To shorten or eliminate this stage, rapid-acting IV agents are given before inhalation anesthesia is administered.
3. Stage III—Surgical anesthesia: There is gradual loss of muscle tone and reflexes as the CNS is further depressed. Regular respiration and relaxation of skeletal muscles with eventual loss of spontaneous movement occur. This is the ideal stage of surgery. Careful monitoring is needed to prevent undesired progression to stage IV.
4. Stage IV—Medullary paralysis: Severe depression of the respiratory and vasomotor centers occurs. Ventilation and/or circulation must be supported to prevent death.



Potency refers to the amount of drug required to produce a certain response. A drug which produces a certain effect at 5 mg dosage is ten times more potent than a drug which produces the same effect at 50 mg dosage. In other words, potency defines as the dose (ED_{50}) or concentration (EC_{50}) of a drug required to produce 50% of the drugs maximum effect. Relative potency is more important than absolute potency

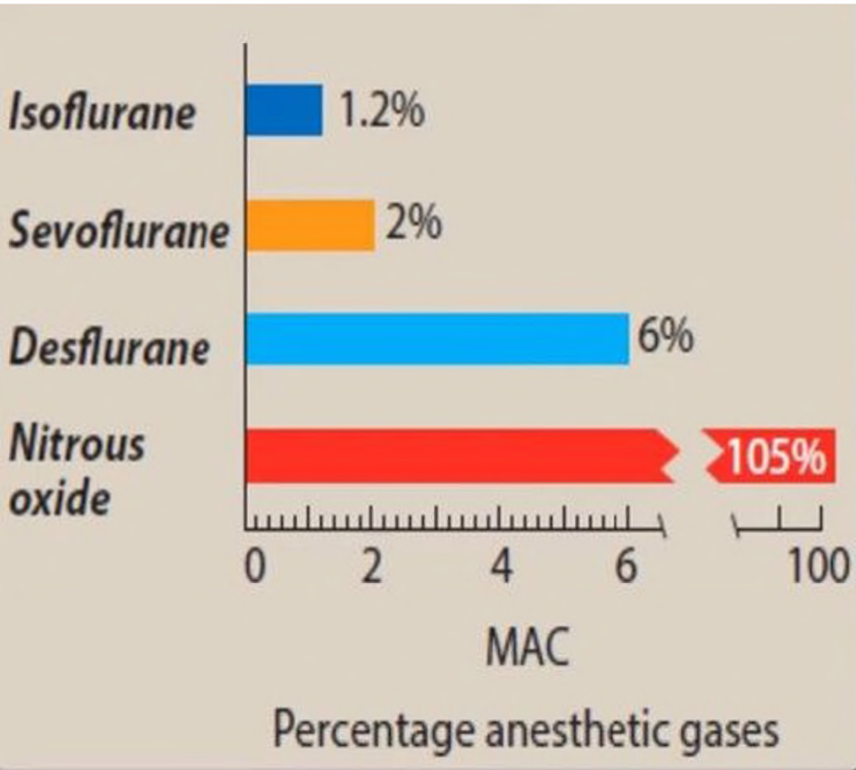


INHALATION ANESTHETICS

Inhaled gases are used primarily for maintenance of anesthesia after administration of an IV drug. Depth of anesthesia can be rapidly altered by changing the inhaled gas concentration. Inhalational agents have steep dose-response curves with very narrow therapeutic indices, so the difference in concentrations from eliciting general anesthesia to cardiopulmonary collapse is small. No antagonists exist. To minimize waste, inhaled gases are delivered in a recirculation system that contains absorbents to remove carbon dioxide and allow rebreathing of the gas.

Potency

Potency is defined quantitatively as the minimum alveolar concentration (MAC), which is the end-tidal concentration of inhaled anesthetic needed to eliminate movement in 50% of patients exposed to a noxious stimulus. MAC is the median effective dose (ED50) of the anesthetic, expressed as the percentage of gas in a mixture required to achieve that effect. Numerically, MAC is small for potent anesthetics



Uptake and distribution of inhalation anesthetics

The principal objective of inhalation anesthesia is a constant and optimal brain partial pressure (P_{br}) of inhaled anesthetic (to create a partial pressure equilibrium between alveoli [P_{alv}] and brain [P_{br}]). Measuring the P_{alv} is the most practical and feasible way to ascertain the P_{br} for the inhaled anesthetic concentration, but this necessitates adequate time for the two compartments to reach equilibrium. The partial pressure of an anesthetic gas that originates by pulmonary entry is the driving force moving the gas from the alveolar space into the bloodstream (P_a), which transports the drug to the brain and other body compartments. Because gases move from one body compartment to another according to partial pressure gradients, a steady state is achieved when the partial pressure in each of these compartments is equivalent to that in the inspired mixture. [Note: At equilibrium, $P_{alv} = P_a = P_{br}$.] The time course for attaining this steady state is determined by the following factors:

1. Alveolar wash-in: This refers to replacement of normal lung gases with the inspired anesthetic mixture. The time required for this process is directly proportional to the functional residual capacity of the lung (volume of gas remaining in the lungs at the end of a normal expiration) and inversely proportional to the ventilator rate. It is independent of the physical properties of the gas. As the partial pressure builds within the lung, anesthetic gas transfer from the lung begins.

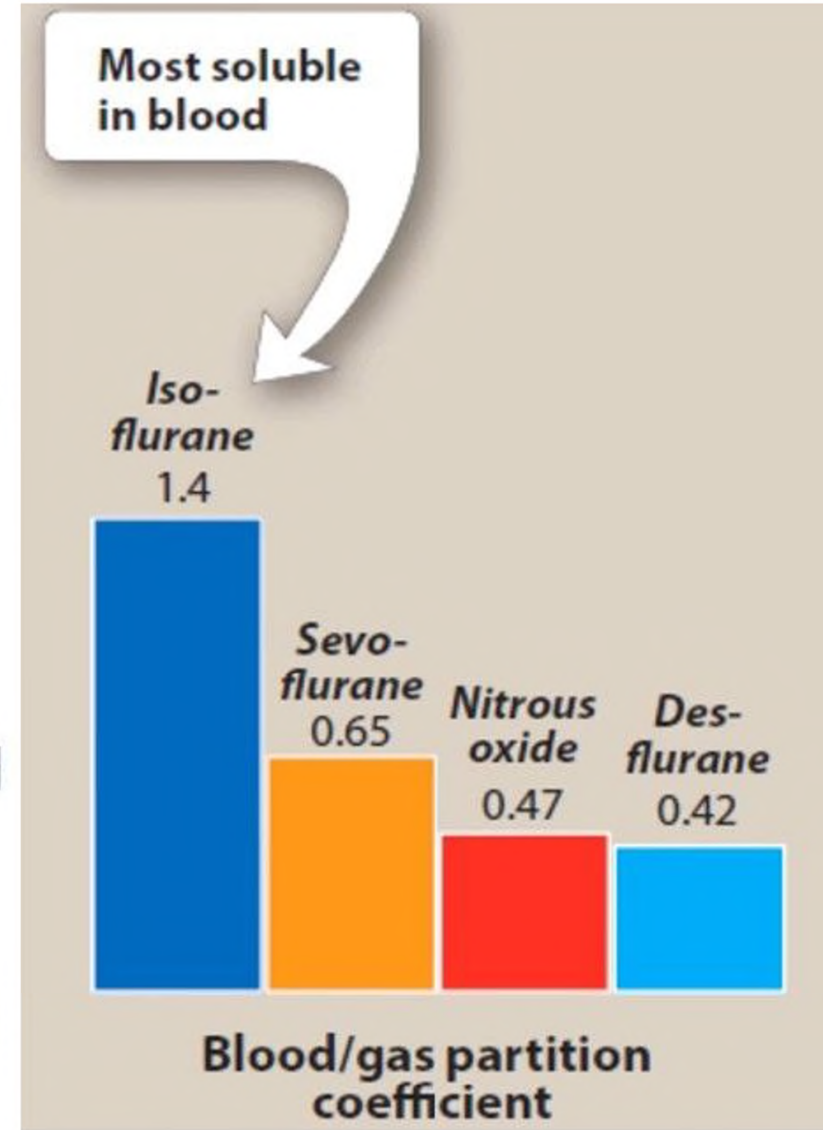
2. Anesthetic uptake (removal to peripheral tissues other than the brain): Uptake is the product of the gas solubility in the blood, cardiac output (CO), and gradient between alveolar and blood anesthetic partial pressures.

Blood:Gas Partition Coefficient



- Solubility is a ratio of concentration of an agent in 2 substances
- The measure of the solubility of an inhalation anesthetic in blood as compared to alveolar gas (air)
- Indication of the speed of induction and recovery for an inhalation anesthetic agent
- Low blood:gas partition coefficient
 - Agent is more soluble in alveolar gas than in blood at equilibrium
 - Agent is less soluble in blood
 - Faster expected induction and recovery

a. Solubility in blood: This is determined by a physical property of the anesthetic called the blood:gas partition coefficient (the ratio of the concentration of anesthetic in the liquid [blood] phase to the concentration of anesthetic in the gas phase when the anesthetic is in equilibrium between the two phases. For inhaled anesthetics, think of the blood as a pharmacologically inactive reservoir. Drugs with low versus high blood solubility differ in their rate of induction of anesthesia. When an anesthetic gas with low blood solubility such as *nitrous oxide* diffuses from the alveoli into the circulation, little anesthetic dissolves in the blood. Therefore, equilibrium between the inspired anesthetic and arterial blood occurs rapidly with relatively few additional molecules



Blood/gas partition coefficients for some inhalation anesthetics

of anesthetic required to raise the arterial anesthetic partial pressure. By contrast, anesthetic gases with high blood solubility, such as *isoflurane*, dissolve more fully in the blood; therefore, greater amounts of gas and longer periods of time are required to raise blood partial pressure. This results in longer periods for induction, recovery, and slower changes in depth of anesthesia in response to changes in the drug concentration. The solubility in blood is ranked as follows: *isoflurane* > *sevoflurane* > *nitrous oxide* > *desflurane*.

b. Cardiac output: CO is inversely correlated with induction time for inhaled anesthetics. This counterintuitive phenomenon is explained by the threshold of drug concentration required to alter neuronal activity and the time neurons are exposed to the drug in the passing blood. During low CO, a longer period of time permits a larger concentration of gas to dissolve in the slowly moving bloodstream. Furthermore, this large bolus of drug has longer contact time to diffuse into neuronal tissue when it traverses the blood–brain barrier. Although a high CO will quickly transport the drug to the brain, a lower concentration of the drug with a shorter exposure time slows down the rate of induction.

c. Alveolar-to-venous partial pressure gradient:

This gradient between the alveolar and returning venous gas partial pressure results from the tissue uptake from the arterial delivery. The arterial circulation distributes the anesthetic to various tissues, and tissue uptake is dependent on the tissue blood flow, blood to tissue partial pressure difference, and blood:tissue solubility coefficient. As venous circulation returns to the lung blood with low or no dissolved anesthetic gas, this high gradient causes gas to move from the alveoli into the blood. If a large alveolar-to-venous partial pressure gradient persists, the peripheral tissue gas uptake must be high, and, therefore, the induction time is longer. Over time, as the partial pressure of gas in venous blood approximates the inspired mixture and subsequent alveolar concentration, no further uptake from the lung occurs.