➢ General and Local Anesthetics

Lecture 3

College of Pharmacy

By:

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- For patients undergoing **surgical or medical procedures**, different levels of sedation can provide important benefits to facilitate procedural interventions.

These levels of sedation range from anxiolysis to general anesthesia and can create:

- Sedation and reduced anxiety
- Lack of awareness and amnesia
- Skeletal muscle relaxation
- Suppression of undesirable reflexes
- Analgesia

Because *no single agent provides all desired objectives, several categories of drugs are combined to produce the optimum level of sedation required (Figure 1).*
Drugs are chosen to provide safe and efficient sedation based on:

- The type and duration of the procedure
- Patient characteristics, such as organ function, medical conditions, and concurrent medications. (Figure 2)

PREOPERATIVE MEDICATIONS
Analgesics
Antacids
Antiemetics
Benzodiazepines*

ANALGESICS
Acetaminophen TYLENOL, OFIRMEV
Celecoxib CELEBREX
Gabapentin NEURONTIN
Ketamine KETALAR*
Opioids (see Chapter 14)

GENERAL ANESTHETICS: INHALED
Desflurane SUPRANE
Isoflurane FORANE
Nitrous oxide GENERIC ONLY
Sevoflurane ULTANE

GENERAL ANESTHETICS: INTRAVENOUS
Dexmedetomidine PRECEDEX
Etomidate AMIDATE
Methohexital BREVITAL
Propofol DIPRIVAN

NEUROMUSCULAR BLOCKERS (see Chapter 5)
Cisatracurium, mivacurium, pancuronium, rocuronium, succinylcholine, vecuronium

LOCAL ANESTHETICS: AMIDES
Bupivacaine MARCAINE
Lidocaine XYLOCAINE
Mepivacaine CARBOCAINE
Ropivacaine NAROPIN

LOCAL ANESTHETICS: ESTERS
Chloroprocaine NESACAINE
Tetracaine GENERIC ONLY

Figure 1: Summary of common drugs used for anesthesia. *Can cause general anesthesia with higher doses.

- **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.

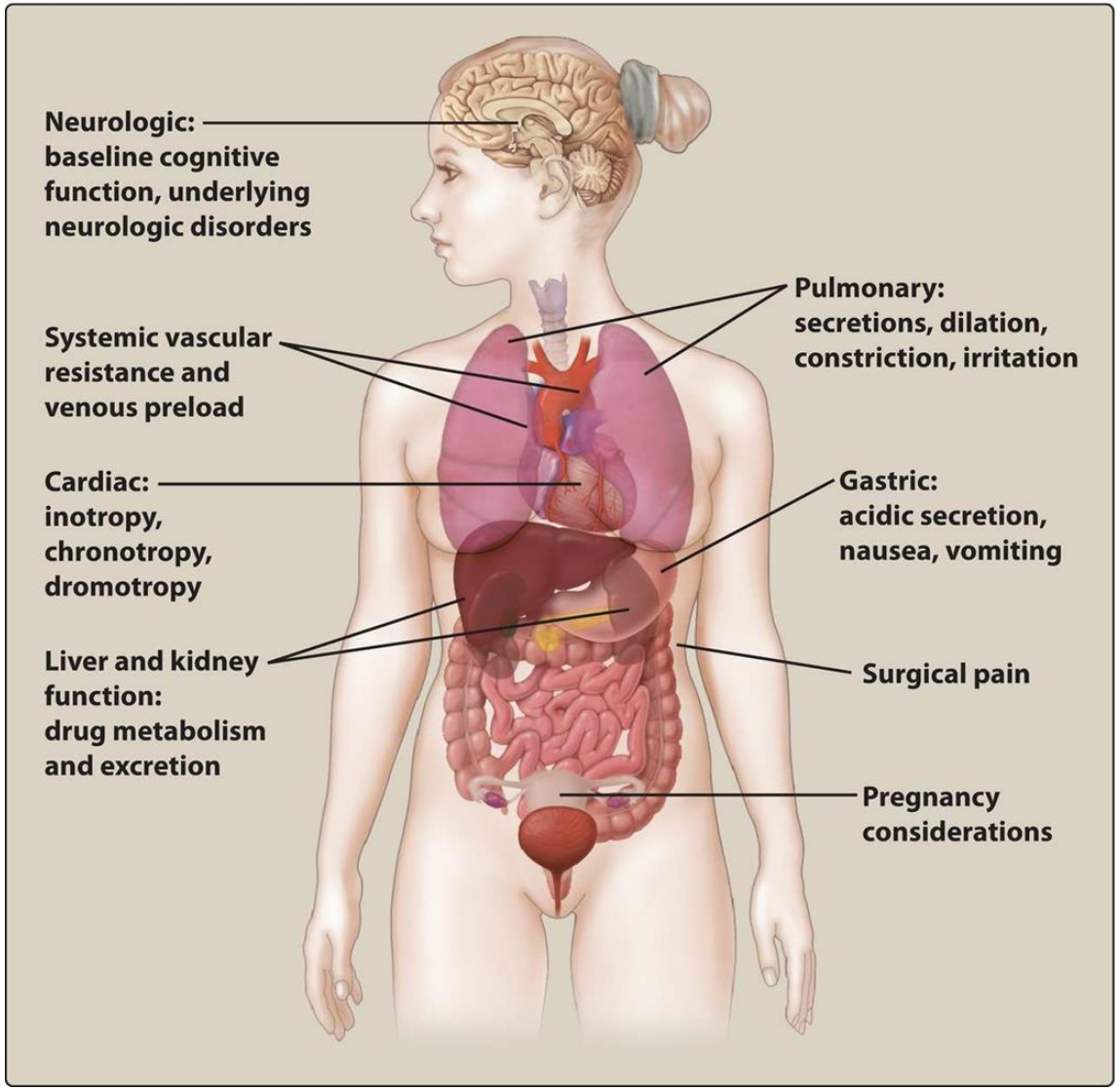


Figure 2: Overall considerations when delivering an anesthetic.

The levels of sedation occur in a dose-related continuum, which is variable and depends on **individual patient response to various drugs**.

	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

Figure 3: Anesthetic levels of sedation.

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:

1- Induction: it is the time from administration of a potent anesthetic to development of unconsciousness. It depends on how fast effective concentrations of anesthetic reach the brain.

2- Maintenance: it is the sustained period of general anesthesia.

3- Recovery: it starts with the discontinuation of the anesthetic and continues until the return of consciousness and protective reflexes. Recovery is essentially the reverse of induction and depends on how fast the anesthetic diffuses from the brain. The patient is monitored to assure full recovery of all normal physiologic functions (spontaneous respiration, blood pressure, heart rate, and all protective reflexes).

❑ 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.

Common features of inhalation anesthetics

- Modern inhalation anesthetics are nonflammable, nonexplosive agents, which include nitrous oxide and volatile, halogenated hydrocarbons.

- These agents decrease cerebrovascular resistance, resulting in increased brain perfusion.

- They cause bronchodilation but also decrease both respiratory drive and hypoxic pulmonary vasoconstriction.

- Movement of these gases from the lungs to various body compartments depends upon their:
- solubility in blood and tissues
- blood flow

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** such as isoflurane and **large for less potent** agents such as nitrous oxide.
- The **more lipid soluble** an anesthetic, **the lower the concentration** needed to produce anesthesia and, therefore, the **higher the potency**.

- Factors that can **increase** MAC (make the patient more **resistant**) include:

hyperthermia, drugs that increase CNS catecholamines, and chronic ethanol abuse.

- Factors that can **decrease** MAC (make the patient more **sensitive**) include:

increased age, hypothermia, pregnancy, sepsis, acute intoxication, concurrent IV anesthetics, and α2-adrenergic receptor agonists (clonidine and dexmedetomidine).

Uptake and distribution of inhalation anesthetics

- 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, **steady state** is achieved when the partial pressure in each of these compartments is equivalent to that in the inspired mixture. [At equilibrium, alveoli (P_{alv})= bloodstream (P_a) = brain ($P_{br.}$)]

The time course for attaining this steady state is determined by the following factors:

1- Alveolar wash-in:

- 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 and inversely proportional to ventilatory rate.
- It is independent of the physical properties of the gas.

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.

a. Solubility in blood
b. Cardiac output
c. Alveolar-to-venous partial pressure gradient of anesthetic

3. Effect of different tissue types on anesthetic uptake

a. Vessel-rich group (brain, heart, liver, kidney, and endocrine glands)

Highly perfused tissues rapidly attain steady state with the partial pressure of anesthetic in the blood.

b. Skeletal muscles

These tissues are moderately perfused with a large storage capacity, which lengthens the time required to achieve steady state.

c. Fat

Fat is poorly perfused but has a very large storage capacity for the highly lipophilic volatile anesthetics. This poor perfusion to a high-capacity compartment drastically prolongs the time required to achieve steady state.

d. Vessel-poor group (bone, ligaments, and cartilage)

These are very poorly perfused and have a low capacity to store anesthetic gas. Therefore, these tissues have minimal impact on the time course of anesthetic distribution in the body.

4. Washout

When an inhalation anesthetic gas is removed from the inspired admixture, the body becomes the repository of anesthetic gas to be circulated back to the alveolar compartment. **The same factors that influence uptake and equilibrium of the inspired anesthetic determine the time course of its exhalation from the body.** Thus, nitrous oxide exits the body faster than does isoflurane (Figure 4).

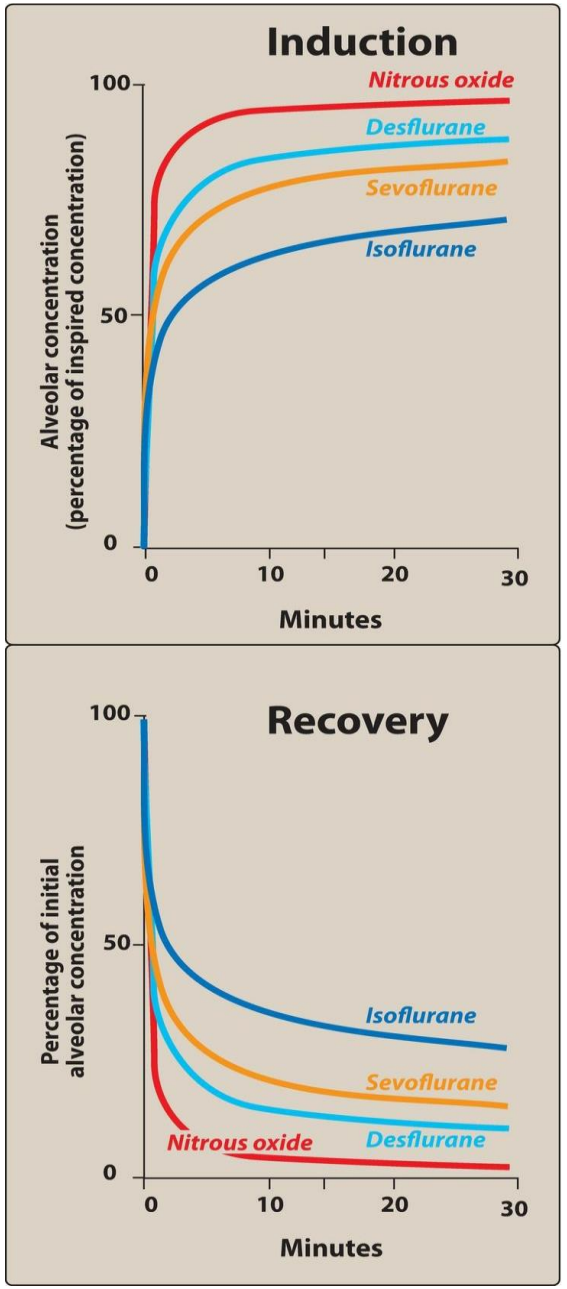
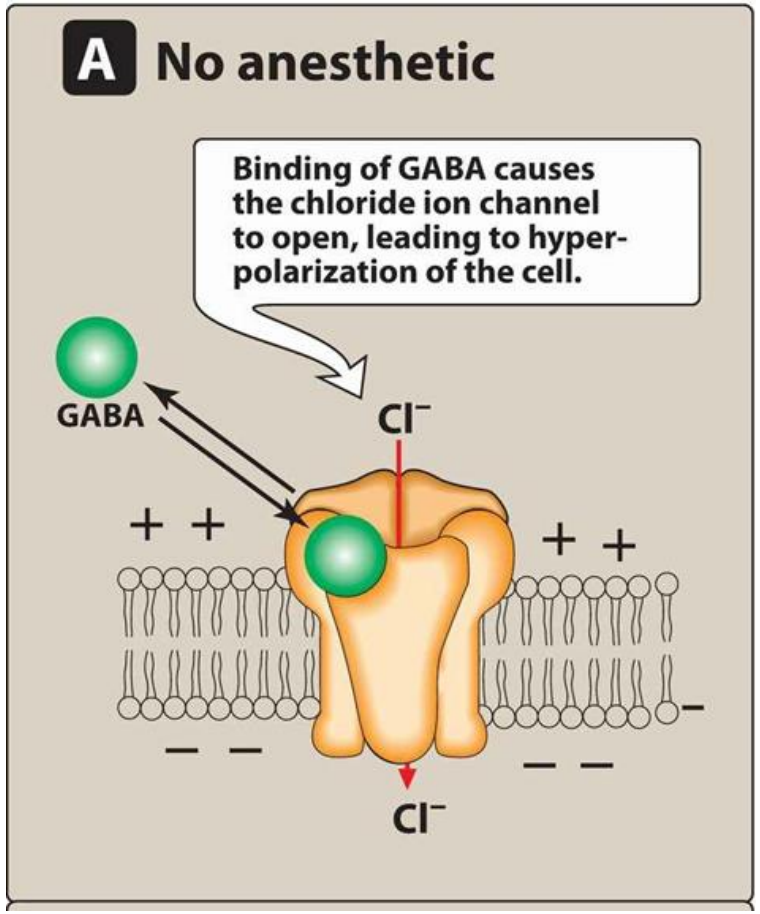


Figure 4: Changes in the alveolar blood concentrations of some inhalation anesthetics over time.

Mechanism of action

- No specific receptor has been identified as the locus to create a state of general anesthesia.
- It appears that a variety of molecular mechanisms may contribute to the activity of anesthetics.

- At clinically effective concentrations, general anesthetics increase the sensitivity of the γ-aminobutyric acid ($GABA_A$) receptors to the inhibitory neurotransmitter GABA.
- This increases chloride ion influx and hyperpolarization of neurons.
- Postsynaptic neuronal excitability and, thus, CNS activity are diminished (Figure 5).
- Unlike other anesthetics, nitrous oxide and ketamine do not have actions on $GABA_A$ receptors. Their effects are mediated via inhibition of N-methyl-D-aspartate (NMDA) receptors. [*The NMDA receptor is a glutamate receptor, which is the body's main excitatory neurotransmitter.*]
- Receptors other than GABA that are affected by volatile anesthetics include the inhibitory glycine receptors found in the spinal motor neurons.
- Additionally, inhalation anesthetics block excitatory postsynaptic currents found on nicotinic receptors. However, the mechanisms by which anesthetics perform these modulatory roles are not fully understood.



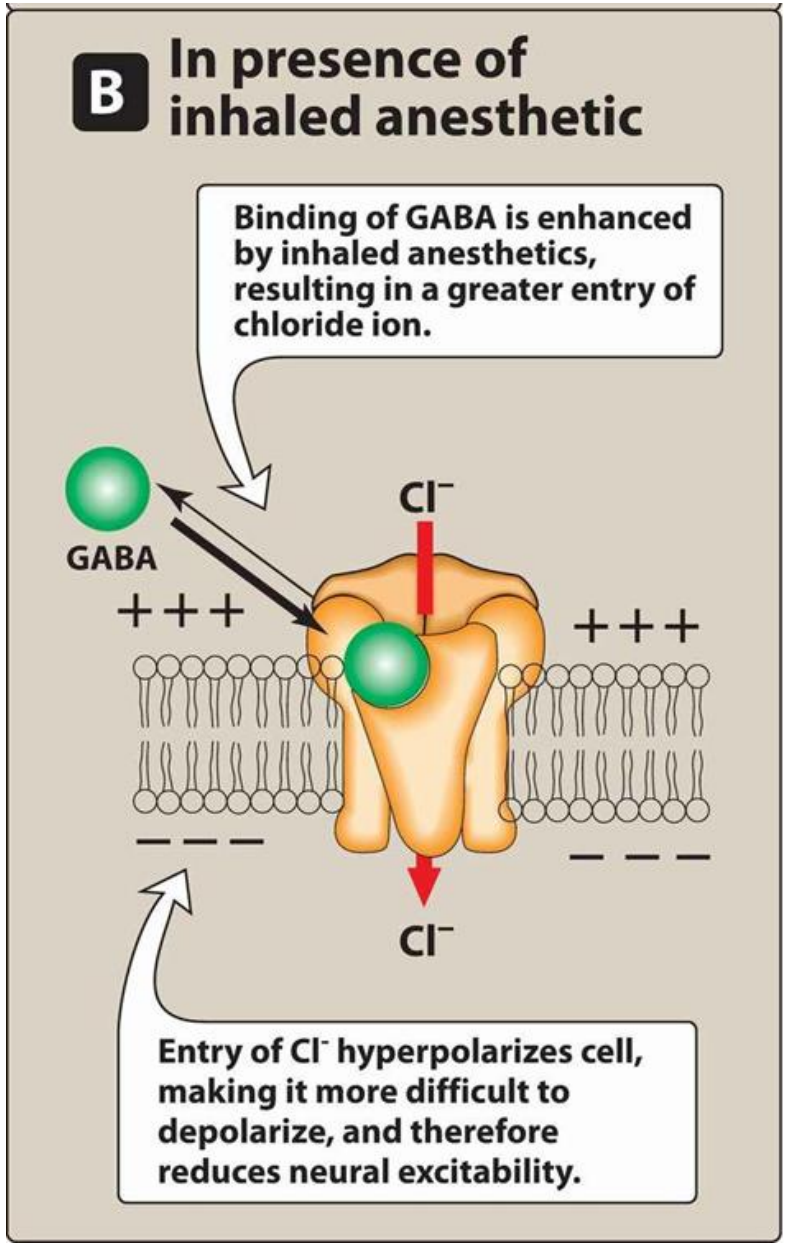


Figure 5: An example of modulation of a ligand-gated membrane channel modulated by inhaled anesthetics. GABA = γ-aminobutyric acid; Cl^- = chloride ion.

➢ Isoflurane

- Isoflurane, like other halogenated gases, produces dose-dependent hypotension predominantly from relaxation of systemic vasculature.
- Hypotension can be treated with a direct-acting vasoconstrictor, such as phenylephrine.
- Because it undergoes little metabolism, isoflurane is considered nontoxic to the liver and kidney.
- Its pungent odor stimulates respiratory reflexes (breath holding, salivation, coughing, laryngospasm), so it is not used for inhalation induction.
- With a higher blood solubility than desflurane and sevoflurane, isoflurane takes longer to reach equilibrium, making it less ideal for short procedures; however, its low cost makes it a good option for longer surgeries.

➢ Desflurane

- Desflurane provides very rapid onset and recovery due to low blood solubility; this makes it a popular anesthetic for short procedures.
- It has a low volatility, which requires administration via a special heated vaporizer.
- Like isoflurane, it decreases vascular resistance and perfuses all major tissues very well.
- It has significant respiratory irritation like isoflurane so it should not be used for inhalation induction.
- Its degradation is minimal and tissue toxicity is rare.
- Higher cost occasionally prohibits its use.

➢ Sevoflurane

- Sevoflurane has low pungency or respiratory irritation. This makes it useful for inhalation induction, especially with pediatric patients who do not tolerate IV placement.
- It has a rapid onset and recovery.
- It has low hepatotoxic potential, but compounds formed from reactions in the anesthesia circuit (soda lime) may be nephrotoxic with very low fresh gas flow that allows longer chemical reaction time.

➢ Nitrous oxide

- Nitrous oxide (“laughing gas”) is a nonirritating potent sedative that is unable to create a state of general anesthesia.
- It is frequently used at concentrations of 30% to 50% in combination with oxygen to create moderate sedation, particularly in dentistry.
- It does not depress respiration, and maintains cardiovascular hemodynamics as well as muscular strength.
- It can be combined with other inhalational agents to establish general anesthesia, which lowers the required concentration of the combined volatile agent.
- This gas admixture further reduces many unwanted side effects of the other volatile agent that impact cardiovascular output and cerebral blood flow.
- Nitrous oxide is poorly soluble in blood and other tissues, allowing it to move very rapidly in and out of the body; this can be problematic in closed body compartments because nitrous oxide can increase the volume (exacerbating a pneumothorax) or pressure (sinus or middle ear pressure).
- Its speed of movement allows nitrous oxide to retard oxygen uptake during recovery, thereby causing “diffusion hypoxia.” This can be overcome by delivering high concentrations of inspired oxygen during recovery.

Some characteristics of the inhalation anesthetics are summarized in Figure 6.

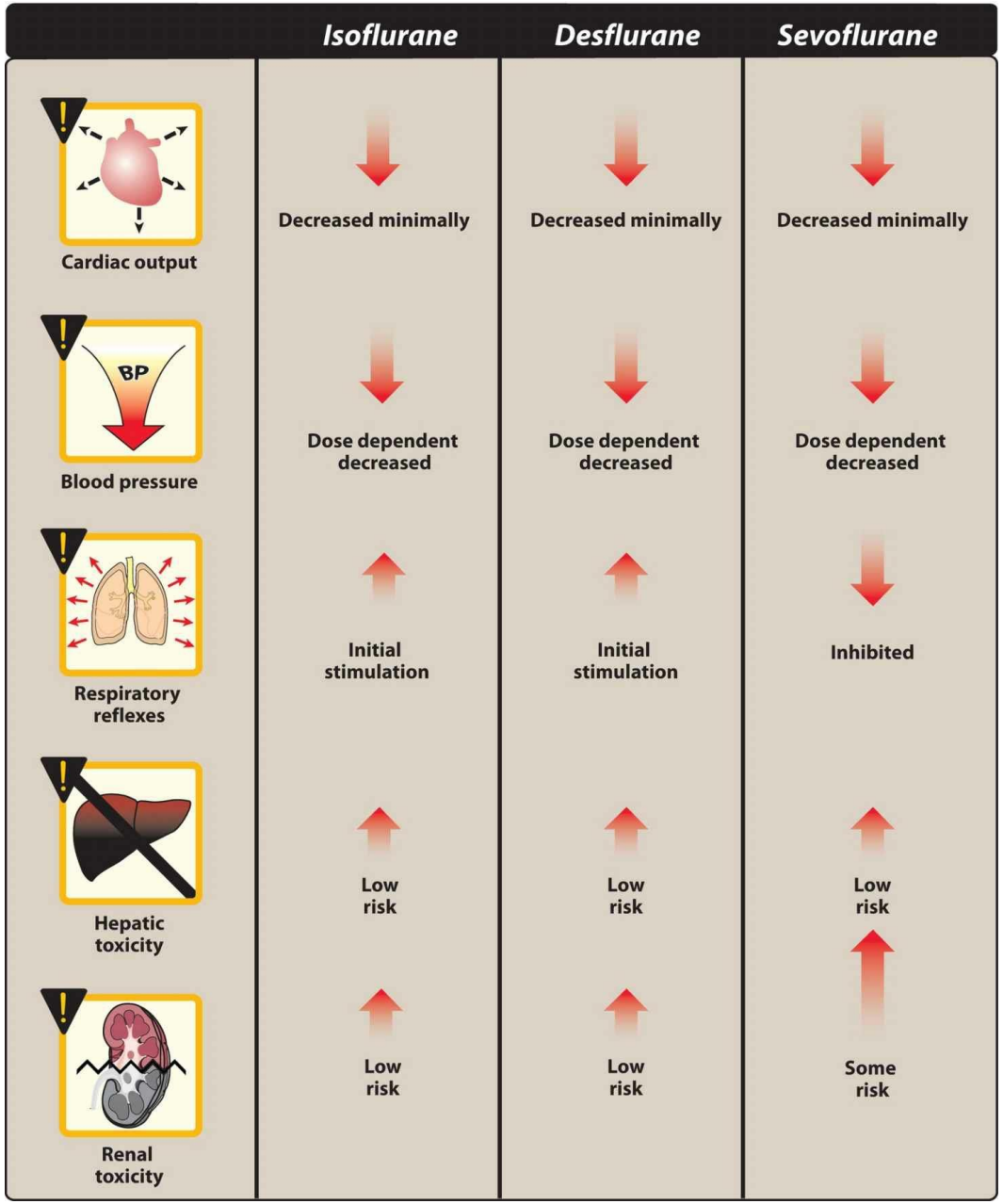


Figure 6: Characteristics of some inhalation anesthetics.

❑ Intravenous Anesthetics

- IV anesthetics **cause rapid induction of anesthesia often occurring in 1 minute or less**.
- It is the most common way to induce anesthesia before maintenance of anesthesia with an inhalation agent.
- IV anesthetics may be used as single agents for short procedures or administered as infusions (TIVA) to help maintain anesthesia during longer surgeries.
- In lower doses, they may be used solely for sedation.

➢ Propofol

- Propofol **is an IV sedative/hypnotic used for induction and/or maintenance of anesthesia**.
- It is widely used and has replaced thiopental as the first choice for induction of general anesthesia and sedation.
- Because propofol is poorly water soluble, it is supplied as an emulsion containing soybean oil and egg phospholipid, giving it a milk like appearance.

1. Onset

- Induction is smooth and occurs 30 to 40 seconds after administration.
- Plasma levels decline rapidly as a result of redistribution
- The initial half-life is 2 to 4 minutes.
- The pharmacokinetics of propofol are not altered by moderate hepatic or renal failure.

2. Actions

- Although propofol depresses the CNS, it occasionally contributes to excitatory phenomena, such as muscle twitching, spontaneous movement, yawning, and hiccups.
- Propofol decreases blood pressure without significantly depressing the myocardium.
- It also reduces intracranial pressure, mainly due to decreased cerebral blood flow and oxygen consumption.
- It has less of a depressant effect than volatile anesthetics on CNS-evoked potentials, making it useful for surgeries in which spinal cord function is monitored.
- It does not provide analgesia, so supplementation with narcotics is required.
- The incidence of postoperative nausea and vomiting (PONV) is very low secondary to its antiemetic properties.

➢ Barbiturates

- Thiopental is an ultra–short-acting barbiturate with high lipid solubility; it is a potent anesthetic but a weak analgesic.
- When given IV, agents such as thiopental and methohexital quickly enter the CNS and depress function, often in less than 1 minute. However, diffusion out of the brain can also occur very rapidly because of redistribution to other tissues.
- These drugs may remain in the body for relatively long periods, because only about 15% of a dose entering the circulation is metabolized by the liver per hour.
- Thus, metabolism of thiopental is much slower than its redistribution.
- Barbiturates tend to decrease blood pressure, which may cause a reflex tachycardia.
- They decrease intracranial pressure through reductions in cerebral blood flow and oxygen consumption.
- Thiopental is no longer available in many countries, including the United States.
- Methohexital is still commonly used for electroconvulsive therapy.

➢ Benzodiazepines

The benzodiazepines are used in conjunction with anesthetics for sedation and amnesia. (for more information, see lecture 2 (Hallucinogens; Anxiolytic and Hypnotic drugs).

➢ Opioids

- Because of their **analgesic property**, opioids are commonly combined with other anesthetics.
- The choice of opioid is based primarily on the duration of action needed.
- The most commonly used opioids are fentanyl and its congeners, sufentanil and remifentanil, because they induce analgesia more rapidly than morphine.
- They may be administered intravenously, epidurally, or intrathecally (into the cerebrospinal fluid).
- Opioids are not good amnestics, and they can all cause hypotension and respiratory depression, as well as nausea and vomiting.
- Opioid effects can be antagonized by naloxone.

➢ Etomidate

- Etomidate is a hypnotic agent used to induce anesthesia, but it lacks analgesic activity.
- Its water solubility is poor, so it is formulated in a propylene glycol solution.
- Induction is rapid, and the drug is short-acting.
- It is usually only used for patients with cardiovascular dysfunction or patients who are acutely critically ill.
- **It inhibits 11-β hydroxylase involved in steroidogenesis**.

Adverse effects may include:

- Decreased plasma cortisol and aldosterone levels.
- It should not be infused for an extended time, because prolonged suppression of these hormones is dangerous.
- Injection site pain, involuntary skeletal muscle movements, and nausea and vomiting are common.

➢ Ketamine

- Ketamine, **a short-acting anti-NMDA receptor anesthetic and analgesic**, induces a dissociated state in which the patient is unconscious (but may appear to be awake) with profound analgesia.
- Ketamine stimulates central sympathetic outflow, causing stimulation of the heart with increased blood pressure and CO

- It is also a potent bronchodilator. Therefore, it is beneficial in patients with hypovolemic or cardiogenic shock as well as asthmatics.
- Conversely, it is contraindicated in hypertensive or stroke patients.
- The drug is lipophilic and enters the brain very quickly. Like the barbiturates, it redistributes to other organs and tissues.
- Ketamine has become popular as an adjunct to reduce opioid consumption during surgery.
- Of note, it may induce hallucinations, particularly in young adults, but pretreatment with benzodiazepines may help.
- Ketamine may be used illicitly, since it causes a dreamlike state and hallucinations similar to phencyclidine (PCP).

➢ Dexmedetomidine

- Dexmedetomidine is a sedative used in intensive care settings and surgery.
- Like clonidine, it is an **α2 receptor agonist in certain parts of the brain**; it 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.
- It has gained popularity for its ability to blunt emergence delirium in the pediatric population.

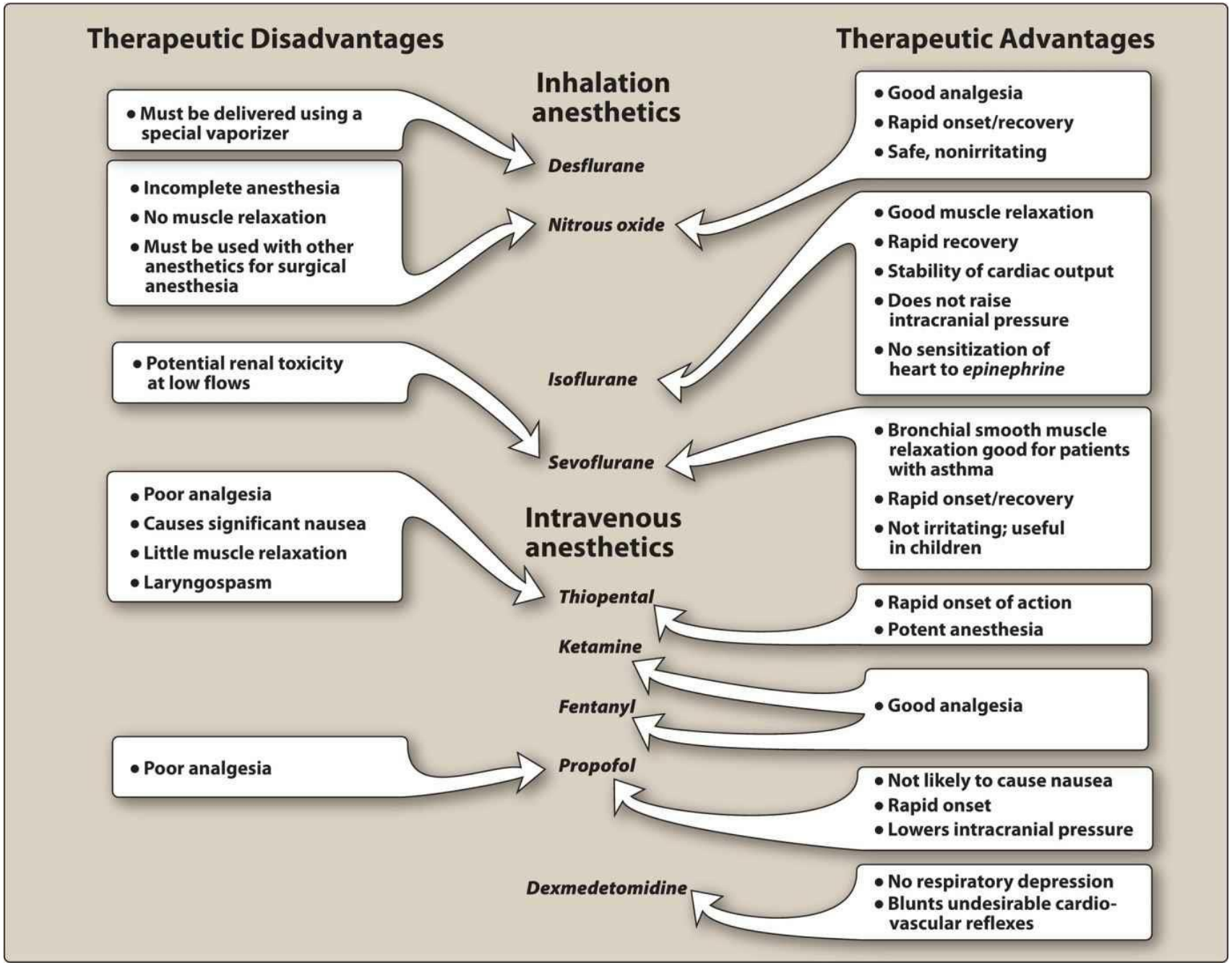


Figure 7: Therapeutic disadvantages and advantages of some anesthetic agents

❑ Neuromuscular Blockers

- Neuromuscular blockers are crucial to the practice of anesthesia and used to:
  - facilitate endotracheal intubation
  - provide muscle relaxation when needed for surgery

- Their mechanism of action is via **blockade of nicotinic acetylcholine receptors on the skeletal muscle cell membrane.** These agents include cisatracurium, mivacurium, pancuronium, rocuronium, succinylcholine, and vecuronium.

❑ Local Anesthetics

- Local anesthetics block nerve conduction of sensory impulses and in higher concentrations block motor impulses from the periphery to the CNS.
- Sodium ion channels are blocked to prevent the transient increase in permeability of the nerve membrane to Na^+ that is required for an action potential (Figure 8).
- When propagation of action potentials is prevented, sensation cannot be transmitted from the source of stimulation to the brain.

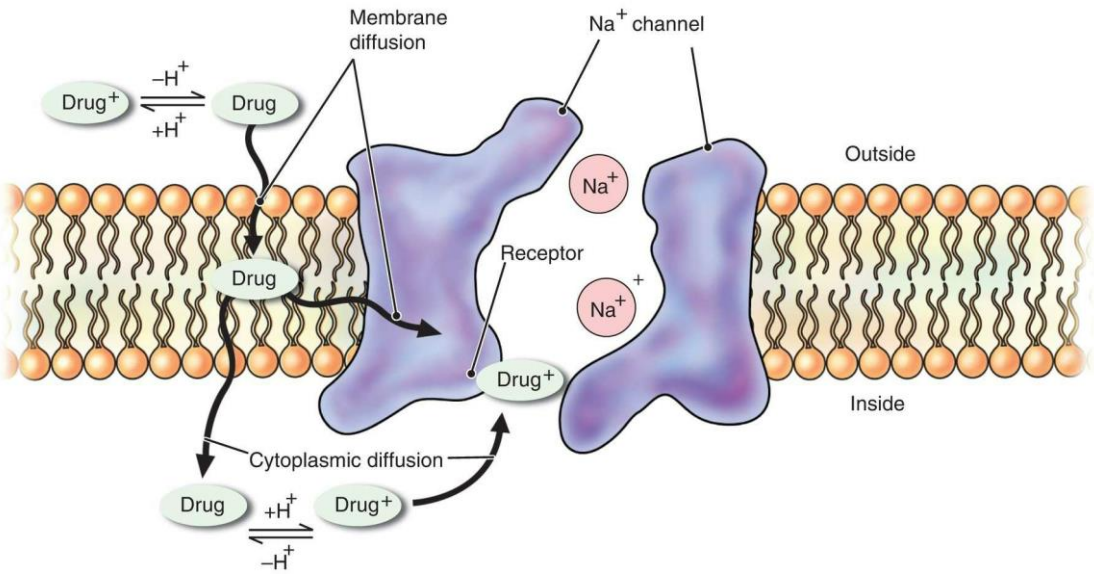


Figure 8: Mechanism of local anesthetic action

- Delivery techniques include topical administration, infiltration, and perineural and neuraxial (spinal, epidural, or caudal) blocks.
- Small, unmyelinated nerve fibers for pain, temperature, and autonomic activity are most sensitive.
- Structurally, local anesthetics all include a lipophilic group joined by an amide or ester linkage to a carbon chain, which, in turn, is joined to a hydrophilic group.
- The most widely used local anesthetics are bupivacaine, lidocaine, mepivacaine, ropivacaine, and tetracaine.

A. Actions

- Local anesthetics cause vasodilation, which leads to a rapid diffusion away from the site of action and short duration when these drugs are administered alone.
- By adding the vasoconstrictor epinephrine, the rate of local anesthetic absorption and diffusion is decreased. This minimizes systemic toxicity and increases the duration of action.
- Hepatic function does not affect the duration of action of local anesthesia because that is determined by redistribution rather than biotransformation.
- Some local anesthetics have other therapeutic uses (for example, lidocaine is an IV antiarrhythmic).

B. Onset, potency, and duration of action

- The onset of action of local anesthetics is influenced by several factors including: tissue pH, nerve morphology, concentration, pKa, and lipid solubility of the drug.
- Local anesthetics with a lower pKa have a quicker onset, since more drug exists in the unionized form at physiologic pH, thereby allowing penetration of the nerve cell membrane.
- Once at the nerve membrane, the ionized form interacts with the protein receptor of the Na^+ channel to inhibit its function and achieve local anesthesia.
- The pH may drop in infected sites, causing onset to be delayed or even prevented.
- Potency and duration of these agents depend mainly on lipid solubility, with higher solubility correlating with increased potency and duration of action.

C. Metabolism

- Biotransformation of amides occurs primarily in the liver.
- Prilocaine, a dental anesthetic, is also metabolized in the plasma and kidney, and one of its metabolites may lead to methemoglobinemia.
- Esters are biotransformed by plasma cholinesterase (pseudocholinesterase).
- Patients with pseudocholinesterase deficiency may metabolize ester local anesthetics more slowly.
- Reduced hepatic function predisposes patients to toxic effects, but should not significantly increase the duration of action of local anesthetics.

D. Allergic reactions

- Patient reports of allergic reactions to local anesthetics are fairly common, but often times, reported “allergies” are actually side effects from the coadministered epinephrine.
- True allergy to an amide local anesthetic is exceedingly rare, while the ester procaine is more allergenic and has largely been removed from the market. Allergy to one ester rules out use of another ester, because the allergenic component is the metabolite para-aminobenzoic acid, produced by all esters.
- By contrast, allergy to one amide does not rule out the use of another amide. A patient may be allergic to other compounds in the local anesthetic, such as preservatives in multidose vials.

E. Local anesthetic systemic toxicity

- Toxic blood levels of a local anesthetic may be due to repeated injections or could result from a single inadvertent IV injection.
- Each drug has a weight-based toxic threshold that should be calculated. This is especially important in children, the elderly, and women in labor (who are more susceptible to local anesthetics).
- Aspiration before every injection is imperative.
- The signs, symptoms, and timing of local anesthetic systemic toxicity (LAST) are unpredictable. One must consider the diagnosis in any patient with altered mental status, seizures, or cardiovascular instability following injection of local anesthetic.
- Treatment for LAST may include seizure suppression, airway management, and cardiopulmonary support.
- Administering a 20% lipid emulsion infusion (lipid rescue therapy) is a valuable asset. Figure 9 summarizes pharmacologic properties of some local anesthetics.

CHARACTERISTIC	ESTERS • *Benzocaine* • *Chloroprocaine* • *Cocaine* • *Procaine* • *Tetracaine*	AMIDES • *Bupivacaine* • *Lidocaine* • *Mepivacaine* • *Prilocaine* • *Ropivacaine*
Metabolism	Rapid by plasma cholinesterase	Slow, hepatic
Systemic toxicity	Less likely	More likely
Allergic reaction	Possible—PABA derivatives form	Very rare
Stability in solution	Breaks down in ampules (heat, sun)	Very stable chemically
Onset of action	Slow as a general rule	Moderate to fast
pKa	Higher than physiologic pH (8.5–8.9)	Close to physiologic pH (7.6–8.1)

DRUG	POTENCY	ONSET	DURATION
Bupivacaine	High	Slow	Long
Chloroprocaine	Low	Rapid	Short
Lidocaine	Low	Rapid	Intermediate
Mepivacaine	Low	Moderate	Intermediate
Procaine	Low	Rapid	Short
Ropivacaine	High	Moderate	Long
Tetracaine	High	Slow	Long (spinal)

Figure 9: Summary of pharmacologic properties of some local anesthetics. PABA = para-aminobenzoic acid.

❑ Anesthetic Adjuncts

- Adjuncts are a critical part of the practice of anesthesia and include drugs that affect gastrointestinal (GI) motility, PONV, anxiety, and analgesia.
- Adjuncts are used in collaboration to help make the anesthetic experience safe and pleasant.

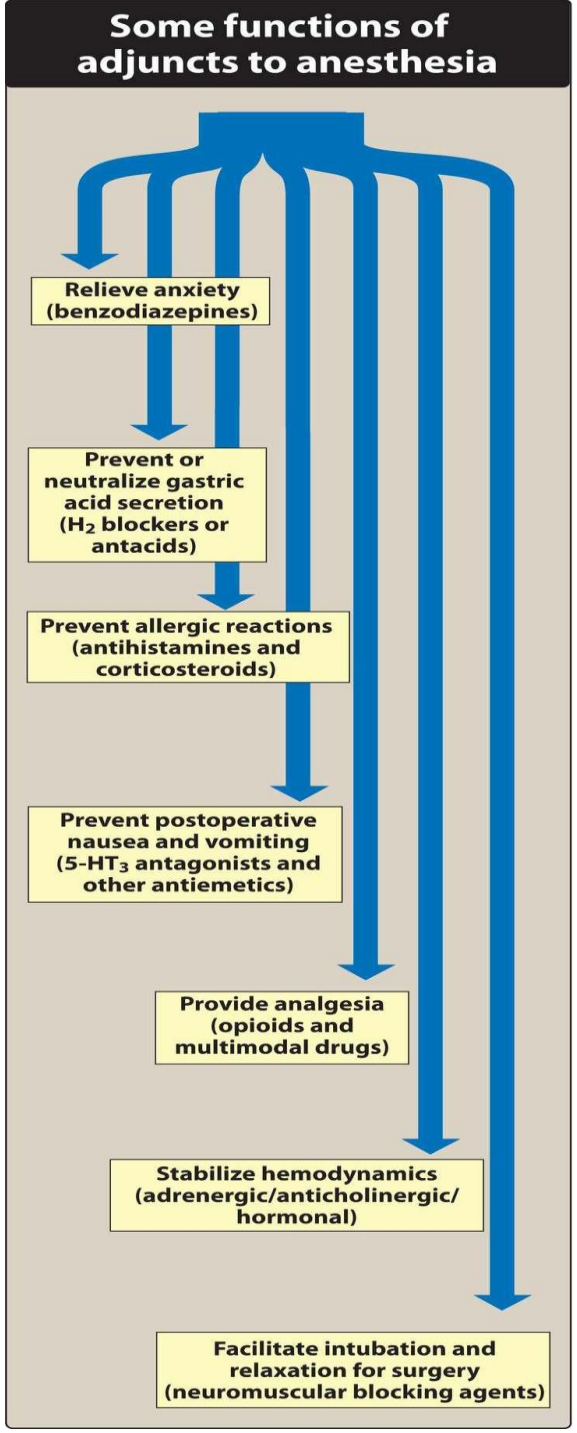


Figure 10: Actions of anesthesia adjunct drugs.


Thank You!