Anesthetics

Overview

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 13.1).
- ☐ 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 (Figure 13.2).
- ☐ 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.

LEVELS OF SEDATION

- The levels of sedation occur in a dose-related continuum, which is variable and depends on individual patient response to various drugs.
- These **"artificial"** levels of sedation start with light sedation (anxiolysis) and continue to moderate sedation, then deep sedation, and finally a state of general anesthesia.
- The hallmarks of escalation from one level to the next are recognized by changes in mentation, hemodynamic stability, and respiratory competency (Figure 13.3). This escalation in levels is often very subtle and unpredictable; therefore, the sedation provider must always be ready to manage the unanticipated next level 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: 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 like *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 like *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).

Inhalation Anesthetics

- Inhaled gases are used primarily for maintenance of anesthesia after administration of an IV drug (Figure 13.4).
- 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.
- Recently, there has been greater attention to the anthropogenic emissions of these potent greenhouse gases, which are typically released from hospital rooftops after each procedure.

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 (increased pulmonary vascular resistance in poorly oxygenated regions of the lungs, redirecting blood flow to better oxygenated regions).
- Movement of these gases from the lungs to various body compartments depends upon their **solubility in blood and tissues**, as well as on **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*. Thus, the inverse of MAC is an index of potency (Figure 13.5).
- *Nitrous oxide* alone cannot produce general anesthesia because any admixture with a survivable oxygen percentage cannot reach its MAC value.
- 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 catechol amines, 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 principal objective of inhalation anesthesia is **a constant and optimal brain partial pressure** (Pbr) of inhaled anesthetic (to create a partial pressure equilibrium between alveoli [Palv] and brain [Pbr]).
- Measuring the Palv is the most practical and feasible way to ascertain the Pbr 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 (Pa), 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.

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 ventilatory 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 g**radient between alveolar and blood anesthetic partial pressure**s.

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; Figure 13.6).
- 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 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 time to change 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-to-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.

3. Effect of different tissue types on anesthetic uptake

- ☐ The time required for a tissue compartment to reach steady state with the partial pressure of the inspired anesthetic gas is inversely proportional to the blood flow to that tissue (greater flow equals less time to reach equilibrium).
- ☐ Time to steady state is directly proportional to the capacity of that tissue to store anesthetic (greater storage capacity equals longer time to reach equilibrium).
- ☐ Furthermore, capacity is directly proportional to the volume of tissue and the tissue:blood solubility coefficient of the gas.

Four major tissue compartments determine the time course of 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 13.7).

Mechanism of action

- ✓ 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 13.8).
- ✓ Unlike other anesthetics, *nitrous oxide* and *ketamine* do not have actions on GABAA receptors. Their effects are mediated via inhibition of *N*-methyl-D-aspartate **(NMDA)** receptors. [Note: 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.

Isoflurane

- *Isoflurane* [eye-so-FLOOR-ane], 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* [DES-floor-ane] 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.
- *Desflurane* 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* [see-voe-FLOOR-ane] 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 due to low blood solubility.
- *Sevoflurane* 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* [NYE-truss OX-ide] (“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.
- *Nitrous oxide* does not depress respiration, and maintains cardiovascular hemodynamics as well as muscular strength.
- *Nitrous oxide* 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.
- Some characteristics of the inhalation anesthetics are summarized in Figure 13.9.

Malignant hyperthermia

☹ In a very small percentage of susceptible patients, exposure to halogenated hydrocarbon anesthetics (or *succinylcholine*) may induce malignant hyperthermia (MH), a rare life-threatening condition.

☹ MH causes a drastic and uncontrolled increase in skeletal muscle oxidative metabolism, overwhelming the body's capacity to supply oxygen, remove carbon dioxide, and regulate temperature, eventually leading to circulatory collapse and death if not treated immediately.

☹ Strong evidence indicates that MH is due to an excitation–contraction coupling defect.

☹ Burn victims and individuals with muscular dystrophy, myopathy, myotonia, and osteogenesis imperfecta are susceptible to MH-like events and caution should be taken.

☹ Susceptibility to MH is often inherited as an autosomal dominant disorder.

☹ patient exhibit symptoms of MH, *dantrolene* is given (also anesthetic admixture is withdrawn) and measures are taken rapidly to cool the patient.

☹ ***Dantrolene*** [DAN-troe-leen] blocks release of Ca2+ from the sarcoplasmic reticulum of muscle cells, reducing heat production and relaxing muscle tone.

☹ Use of *dantrolene* and avoidance of triggering agents such as halogenated anesthetics in susceptible individuals have markedly reduced mortality from MH.

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.

A. Induction

☑ After entering the blood, a percentage of drug binds to plasma proteins, and the rest remains unbound or “free.”

- ☑ The degree of protein binding depends upon the physical characteristics of the drug, such as the degree of ionization and lipid solubility.
- ☑ The majority of CO flows to the brain, liver, and kidney (“vessel-rich organs”). Thus, a high proportion of initial drug bolus is delivered to the cerebral circulation and then passes along a concentration gradient from blood into the brain.
- ☑ The rate of this transfer is dependent on the arterial concentration of the unbound free drug, the lipid solubility of the drug, and the degree of ionization.
- ☑ Unbound, lipid-soluble, nonionized molecules cross into the brain most quickly.
- ☑ Like inhalational anesthetics, mode of action of IV anesthetics , GABA likely plays a large role.

B. Recovery

- ☑ Recovery from IV anesthetics is due to redistribution from the CNS. After initial flooding of the CNS and other vessel-rich tissues with nonionized molecules, the drug diffuses into other tissues with less blood supply.
- ☑ With secondary tissue uptake, predominantly skeletal muscle, plasma concentration of the drug falls. This allows the drug to diffuse out of the CNS, down the resulting reverse concentration gradient.
- ☑ This initial redistribution of drug into other tissues leads to the rapid recovery seen after a single IV dose of induction agent.
- ☑ Metabolism and plasma clearance become important only following infusions and repeat doses of a drug.

☑ Adipose tissue makes little contribution to the early redistribution of free drug following a bolus, due to its poor blood supply. However, following repeat doses or infusions, equilibration with fat tissue forms a drug reservoir, often leading to delayed recovery.

C. Effect of reduced cardiac output on IV anesthetics

☑ When CO is reduced (for example, in certain types of shock, the elderly, cardiac disease), the body compensates by diverting more CO to the cerebral circulation.

☑ A greater proportion of the IV anesthetic enters the cerebral circulation under these circumstances. Therefore, the dose of the drug must be reduced. Further, decreased CO causes prolonged circulation time.

☑ As global CO is reduced, it takes a longer time for an induction drug to reach the brain and exert its effects.

☑ **The slow titration of a reduced dose of an IV anesthetic is key to a safe induction in patients with reduced CO.**

Propofol

- *Propofol* [PRO-puh-fol] 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 milklike appearance.

1. Onset

- Induction is smooth and occurs 30 to 40 seconds after administration.

- Plasma levels decline rapidly as a result of redistribution, followed by a more prolonged period of hepatic metabolism and renal clearance.
- The initial redistribution 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.
- Transient pain at the injection site is common.
- *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.
- *Propofol* is commonly infused in lower doses to provide sedation.
- The incidence of postoperative nausea and vomiting (PONV) is very low secondary to its antiemetic properties.

Barbiturates

- *Thiopental* [THYE-oh-PEN-tahl] is an ultra–short-acting barbiturate with high lipid solubility.
- It is a potent anesthetic but a weak analgesic.

- Barbiturates require supplementary analgesic administration during anesthesia.
- When given IV, agents such as *thiopental* and *methohexital* [meth-oh-HEX-uh-tall] 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 (Figure 13.10).
- 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.
- The most commonly used is ***midazolam*** [meh-DAZ-o-lam].
- ***Diazepam*** [dye-AZ-uh-pam] and ***lorazepam*** [lore-AZ-uh-pam] are alternatives.

- All three facilitate amnesia while causing sedation, enhancing the inhibitory effects of various neurotransmitters, particularly GABA.
- Minimal cardiovascular depressant effects are seen, but all are potential respiratory depressants (especially when administered IV).
- They are metabolized by the liver with variable elimination half-lives, and *erythromycin* may prolong effects of *midazolam*.
- Benzodiazepines can induce a temporary form of anterograde amnesia in which the patient retains memory of past events, but new information is not transferred into long-term memory. Therefore, important treatment information should be repeated to the patient after the effects of the drug have worn off.

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*** **[**FEN-ta-nil] and its congeners, ***sufentanil*** [SOO-fen-ta-nil] and ***remifentanil*** [REMI-fen-ta-nil], 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* [ee-TOM-uh-date] 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.
- Among its benefits are little to no effect on the heart and systemic vascular resistance.
- *Etomidate* is usually only used for patients with cardiovascular dysfunction or patients who are acutely critically ill.
- It inhibits 11-β hydroxylase involved in steroidogenesis, and adverse effects may include decreased plasma cortisol and aldosterone levels.
- *Etomidate* 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* [KET-uh-meen], 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* [dex-med-eh-TOM-uh-deen] is a sedative used in intensive care settings and surgery.
- Like *clonidine*, it is an α2 receptor agonist in certain parts of the brain.
- *Dexmedetomidine* 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.
- Some therapeutic advantages and disadvantages of the anesthetic agents are summarized in Figure 13.11.

Neuromuscular Blockers

- ☒ Neuromuscular blockers are crucial to the practice of anesthesia and used to facilitate endotracheal intubation and 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*.

A. Sugammadex

- ☒ *Sugammadex* [soo-GAM-ma-dex] is a selective relaxant-binding agent that terminates the action of both *rocuronium* and *vecuronium*.
- ☒ Its three-dimensional structure traps the neuromuscular blocker in a 1:1 ratio, terminating its action and making it water soluble.
- ☒ It is unique in that it produces rapid and effective reversal of both shallow and profound neuromuscular blockade.
- ☒ *Sugammadex* is eliminated via the kidneys.

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 13.12).
- ☒ When propagation of action potentials is prevented, sensation cannot be transmitted from the source of stimulation to the brain.

- ☒ 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 (Figure 13.13).
- ☒ The most widely used local anesthetics are *bupivacaine* [byoo-PIV-uh-cane], *lidocaine* [LYE-doe-cane], *mepivacaine* [muh-PIV-uh-cane], *ropivacaine* [roe-PIV-uh-cane], and *tetracaine* [TET-truh-cane].

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. Of these, the pKa is most important. 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* [PRY-low-cane], 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.
- ✓ At normal doses, this has little clinical effect. 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 13.14 summarizes pharmacologic properties of some local anesthetics.

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.

Gastrointestinal medications

- H2-receptor antagonists (for example, *ranitidine*;) and proton pump inhibitors (for example,*omeprazole*;) help to reduce gastric acidity in the event of an aspiration.
- Nonparticulate antacids (*sodium citrate*/*citric acid*) are given occasionally to quickly increase the pH of stomach contents. These drugs are used in the obstetric population going to surgery, along with other patients with reflux.
- Finally, a dopamine receptor antagonist (*metoclopramide*) can be used as a prokinetic agent to speed gastric emptying and increase lower esophageal sphincter tone.

Medications for PONV

- PONV can be a significant problem during and after surgery both for the clinician and the patient.
- Risk factors for PONV include female gender, nonsmoker, use of volatile and nitrous anesthetics, duration of surgery, and postoperative narcotic use.
- 5-HT3 receptor antagonists (for example, ***ondansetron***) are commonly used to prevent PONV and are usually administered toward the end of surgery.

- Caution is advised in patients with long QT intervals on electrocardiogram (ECG).
- An anticholinergic and antihistamine (***promethazine***) can also be used; however, sedation, delirium, and confusion can complicate the postoperative period, especially in the elderly.
- Glucocorticoids such as ***dexamethasone*** can be used to reduce PONV.
- The mechanism is unclear, but because of a longer onset, these agents are usually given at the start of surgery. The neurokinin-1 antagonist *aprepitant* has also been shown to reduce PONV.
- Lastly, transdermal *scopolamine* is given preoperatively to patients with multiple risk factors or a history of PONV.
- Caution is advised because it can produce central anticholinergic effects.

Anxiety medications

- Anxiety is a common part of the surgical experience. Benzodiazepines (***midazolam, diazepam***), α2 agonists (*clonidine*, *dexmedetomidine*), and H1-receptor antagonists (*diphenhydramine*) can be used to alleviate anxiety.
- Benzodiazepines also elicit anterograde amnesia, which can help promote a more pleasant surgical experience.

Analgesia

- While opioids are a mainstay in anesthesia for pain control, multimodal analgesia is becoming more common due to the long-term risks of opioid consumption in surgical patients.
- Nonsteroidal anti-inflammatory drugs (*ketorolac*,*celecoxib*;) are common adjuncts to opioids.
- Caution should be used in patients with coagulopathies, and in those with a history of peptic ulcer or platelet aggregation abnormalities.
- *Acetaminophen* can be used both PO and IV, but caution is advised in impaired hepatic function.
- Analogs of GABA (***gabapentin, pregabalin***) are becoming more common as pretreatment to reduce opioid consumption both during and after surgery. They also have multiple uses in neuropathic pain and addiction medicine.
- The **NMDA** antagonist ***ketamine*** is used to reduce overall opioid consumption both intra- and postoperatively. Actions of anesthesia adjunct drugs are shown in Figure 13.15.