Anesthetic Agents: General and Local Anesthetics

Introduction

Anesthesia, defined as a loss of sensation with or without loss of consciousness, can be effectively achieved with a wide range of drugs with very diverse chemical structures. The list of such compounds includes not only the classic anesthetic agents, such as the general and local anesthetics, but also many central nervous system (CNS) depressants, such as analgesics, sedative/hypnotics (barbiturates and benzodiazepines), anticonvulsants, and skeletal muscle relaxants. Many of these agents are routinely used today in clinical practice to facilitate surgical and medical procedures.

Types of Anesthetics:

A- General Anaesthesia:

General anaesthesia is a reversible state of central nervous system (CNS) depression, causing loss of response to and perception of stimuli. For patients undergoing surgical or medical procedures, anaesthesia provides five important benefits:

a- Sedation and reduced anxiety
b- Lack of awareness and amnesia.
c- Skeletal muscle relaxation.
d- Suppression of undesirable reflexes.
e- Analgesia

❖ Because no single agent provides all desirable properties,several categories of drugs are combined to produce optimal anesthesia (**Figure1**).

❖ Preanesthetics help calm patients, relieve pain, and prevent side effects of subsequently administered anesthetics or the procedure itself.

❖ In addition, the neuromuscular blockers facilitate tracheal intubation and surgery.

❖ Potent general anesthetics usually are delivered via inhalation and/or intravenous (IV) injection.

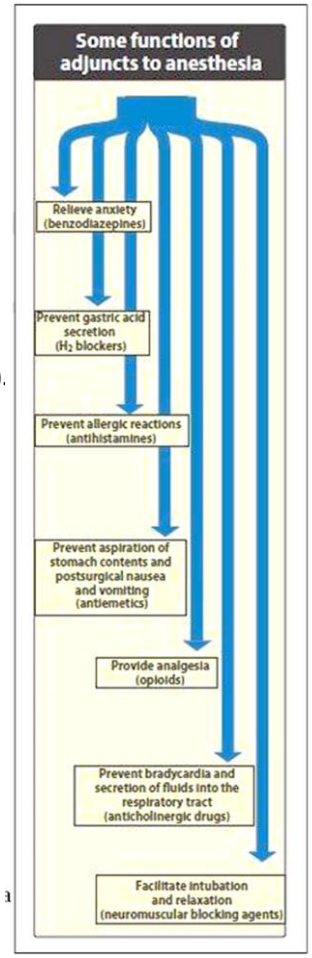

Figure 1: Actions of anesthesia adjunct drugs.

Patient factors in selection of anaesthesia

Drugs are chosen to provide safe and efficient anaesthesia 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: Anaesthetic agents suppress cardiovascular function to varying degrees. So, they should be used with caution in patients with coronary artery disease, heart failure, dysrhythmias, and other cardiovascular disorders. To treat the hypotension, which may develop during anaesthesia and lead to reduce perfusion pressure and ischemic injury to tissues, vasoactive agents may be used . Some anaesthetics, such as halothane, sensitize the heart to arrhythmogenic effects of sympathomimetic agents.

2. 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.

3. Liver and kidney: The liver and kidneys influence long-term distribution and clearance of drugs and are also target organs for toxic effects.

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

5. Pregnancy: Special precautions should be observed when anesthetics and adjunctive agents are administered during pregnancy. Effects on 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: Premedications play an important role in anesthesia as they can facilitate the 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.

2. Concomitant use of other drugs: Patients may take medications for underlying diseases or abuse drugs that alter response to anesthetics. For example, alcoholics have elevated levels of liver enzymes that metabolize anesthetics, and drug abusers may be tolerant to opioids.

STAGES AND DEPTH OF ANESTHESIA

General anesthesia has three stages: **induction**, **maintenance**, and **recovery**. **Induction** is the time from administration of a potent anesthetic to development of effective anesthesia. **Maintenance** provides sustained anesthesia. Recovery is the time from discontinuation of anesthetic until consciousness and protective reflexes return. 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. Depth of anesthesia is the degree to which the CNS is depressed.

A- Induction

General anesthesia in adults is normally induced with an IV agent like propofol, producing unconsciousness in 30 to 40 seconds. Additional inhalation and/or IV drugs may be given to produce the desired depth of anesthesia. [Note: This often includes an IV neuromuscular blocker such as rocuronium, vecuronium, or succinylcholine to facilitate tracheal intubation and muscle relaxation] **Figure 2**.

B. Maintenance of anesthesia

After administering the anesthetic, vital signs and response to stimuli are monitored continuously to balance the amount of drug inhaled and/or infused with the depth of anesthesia. Maintenance is commonly provided with volatile anesthetics, which offer good control over the depth of anesthesia. Opioids such as fentanyl are used for analgesia along with inhalation agents, because the latter are not good analgesics. IV infusions of various drugs may be used during the maintenance phase.

C. Recovery

Postoperatively, the anesthetic admixture is withdrawn, and the patient is monitored for return of consciousness. For most anesthetic agents, recovery is the reverse of induction. Redistribution from the site of action (rather than metabolism of the drug) underlies recovery. If neuromuscular blockers have not been fully metabolised, reversal agents may be used. The patient is monitored to assure full recovery, with normal physiologic functions (spontaneous respiration, acceptable blood pressure and heart rate, intact reflexes, and no delayed reactions such as respiratory depression).

THE 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 diethyl 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— Delirium:** 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 for surgery. Careful monitoring is needed to prevent undesired progression to stage IV.
4. **Stage IV— Respiratory paralysis:** Severe depression of the respiratory and vasomotor centers occurs. Ventilation and/or circulation must be supported to prevent death.

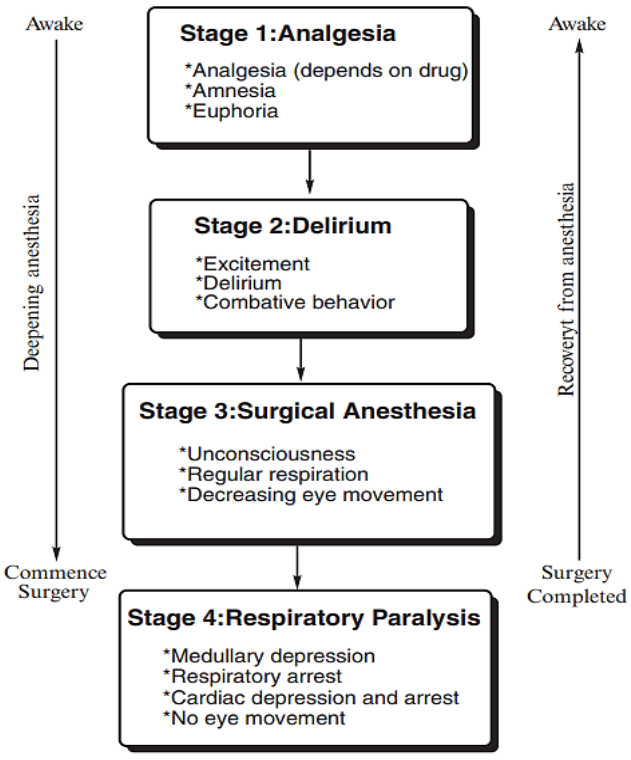

Figure 2: Stages of general anesthesia.

There are 3 different routes of administration of the anaesthetics, which are:

A- INHALATION ANESTHETICS(Volatile)

• Inhaled gases are used primarily for maintenance of anesthesia after administration of an IV agent.

• Depth of anesthesia can be rapidly altered by changing the inhaled concentration. The inhaled anaesthetics are summarised in **Figure 3**.

Figure 3: Inhaled anaesthetics

Common features of inhalation anesthetics:

• Modern inhalation anesthetics are non-flammable, nonexplosive agents.

• They include nitrous oxide and volatile, halogenated hydrocarbons.

• Movement of these agents from the lungs to various body compartments depends upon:

✓ Their solubility in blood and tissues, as well as on blood flow.

✓ The above- mentioned factors play a role in induction and recovery.

Mechanism of action of inhaled anesthetics

❖ Generally, no specific receptor has been identified as the locus of general anesthetic action. The fact that chemically unrelated compounds produce anesthesia argues against the existence of a single receptor.

❖ At clinically effective concentrations, general anesthetics increase the sensitivity of the γ-aminobutyric acid (GABAA) receptors to the inhibitory neurotransmitter GABA. This increases chloride ion influx and hyperpolarization of neurons. Postsynaptic neuronal excitability and, thus, CNS activity are diminished.

❖ Unlike other anesthetics, nitrous oxide and ketamine do not have actions on GABAA receptors. Their effects are likely mediated via inhibition of the N methyl-d-aspartate (NMDA) receptors. [Note: The NMDA receptor is a glutamate receptor. Glutamate is the body's main excitatory neurotransmitter].

a- Halothane

Halothane is the prototype to which newer inhalation anesthetics are compared. When halothane was introduced, its rapid induction and quick recovery made it an anesthetic of choice. Due to adverse effects and the availability of other anesthetics with fewer complications, halothane has been replaced in most countries.

Therapeutic uses

✓ Halothane is a potent anesthetic but a relatively weak analgesic. Thus, it is usually coadministered with nitrous oxide, opioids, or local anesthetics.

✓ Halothane relaxes both skeletal and uterine muscles and can be used in obstetrics when uterine relaxation is indicated.

✓ Halothane is not hepatotoxic in children (unlike its potential effect on adults).

✓ Combined with its pleasant odor, it is suitable in pediatrics for inhalation induction, although sevoflurane is now the agent of choice.

Adverse effects

such as cardiac arrhythmias and produce concentration-dependent hypotension, which can be best treated with a direct-acting vasoconstrictor, such as phenylephrine. Moreover, it can cause Malignant hyperthermia (MH).

b- Nitrous oxide (NO)

• NO (“laughing gas”) is a non-irritating potent analgesic but a weak general anesthetic. It is frequently used at concentrations of 30 to 50% in combination with oxygen for analgesia, particularly in dentistry.

• NO alone cannot produce surgical anesthesia, but it is commonly combined with other more potent agents.

• NO is poorly soluble in blood and other tissues, allowing it to move very rapidly in and out of the body.

• Within closed body compartments, nitrous oxide can increase the volume (for example, causing a pneumothorax) or pressure (for example, in the sinuses), because it replaces nitrogen in various air spaces faster than the nitrogen leaves. Its speed of movement allows nitrous oxide to retard oxygen uptake during recovery, thereby causing “diffusion hypoxia,” which can be overcome by significant concentrations of inspired oxygen during recovery.

• NO does not depress respiration and does not produce muscle relaxation.

• When coadministered with other anesthetics, it has moderate to no effect on the cardiovascular system or on increasing cerebral blood flow, and it is the least hepatotoxic of the inhalation agents.

• Therefore, it is probably the safest of these anesthetics, provided that sufficient oxygen is administered simultaneously.

B- INTRAVENOUS ANESTHETICS

• IV anesthetics cause rapid induction often occurring within one "arm– brain circulation time," or the time it takes to travel from the site of injection (usually the arm) to the brain, where it has its effect.

• Anesthesia may then be maintained with an inhalation agent.

• IV anesthetics may be used as sole agents for short procedures or administered as infusions to help maintain anesthesia during longer cases.

• In lower doses, they may be used for sedation.

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

• Propofol is commonly infused in lower doses to provide sedation.

• The incidence of postoperative nausea and vomiting is very low, as this agent has some antiemetic effects.

2- Barbiturates

• Thiopental 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 quickly enter the CNS and depress function, often in less than 1 minute.

• 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.

• Thiopental has minor effects on the normal cardiovascular system but may contribute to severe hypotension in patients with hypovolemia or shock.

3- Benzodiazepines

• The benzodiazepines are used in conjunction with anesthetics for sedation.

• The most commonly used is midazolam.

• Diazepam and lorazepam are alternatives. All three facilitate amnesia while causing sedation, enhancing the inhibitory effects of various neurotransmitters, particularly GABA.

• 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.

4- 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 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 amnesics, and they can all cause hypotension, respiratory depression, and muscle rigidity, as well as postanesthetic nausea and vomiting.

• Opioid effects can be antagonized by naloxone.

• In addition to the above-mentioned drugs, there are Etomidate, Ketamine, Neuromuscular blockers and Dexmedetomidine.

Their important properties are summarised in figure 4.

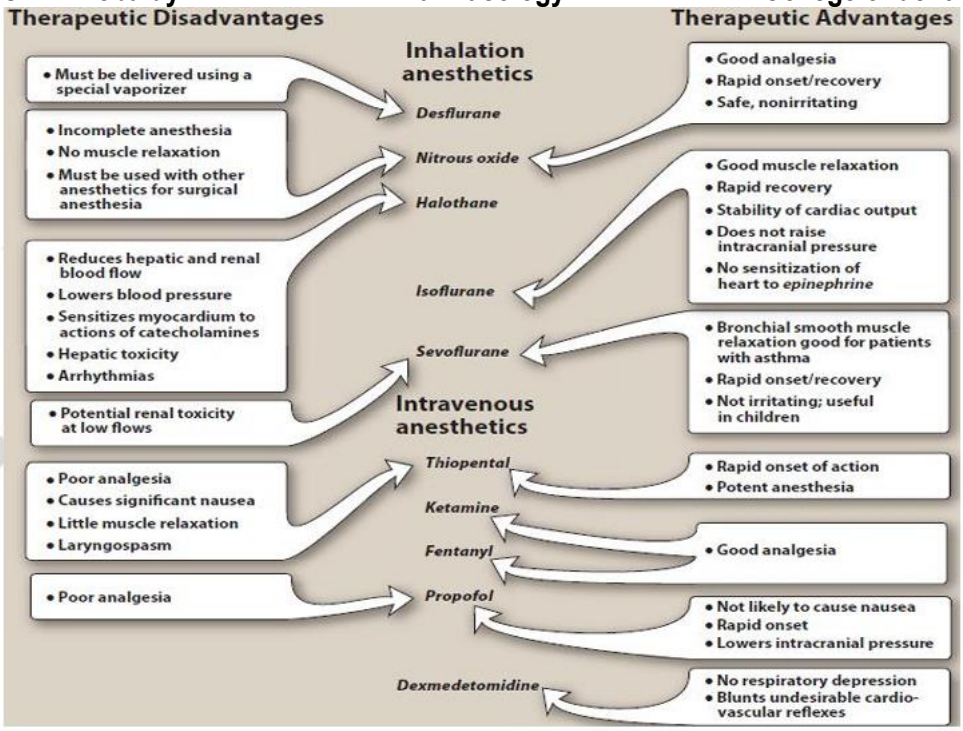

Figure 4: Therapeutic disadvantages and advantages of some anesthetic agents. (MEMORISABLE)

LOCAL ANESTHETICS

Local anesthetic agents are drugs that, when given either topically or administered directly into a localized area, produce a state of local anesthesia by reversibly blocking nerve conductances that transmit the sensations of pain from this localized area to the brain. Unlike the anesthesia produced by general anesthetics, the anesthesia produced by local anesthetics is without loss of consciousness or impairment of vital central cardiorespiratory functions. Local anesthetics block nerve conductance by binding to selective sites on the Na+ channels in the excitable membranes, thereby reducing Na+ passage (i.e., conductance) through the pores and, thus, interfere with the generation of action potentials. Although local anesthetics decrease the excitability of nerve membranes, they do not affect the neuron's resting potential. Local anesthetics, in contrast to analgesic compounds, do not interact with the pain receptors or inhibit the release or the biosynthesis of pain mediators.

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 5**).

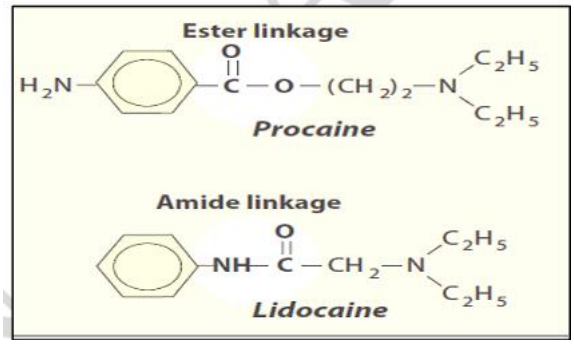

Figure 5: Representative structures of ester and amide anesthetics.

TABLE 16.9 Structures of Local Anesthetics

Amino Esters

Benoxinate (pKa = 9.0)

Benzocaine, R= C_2H_5 (pKa = 2.8)
Butamben, R= n-C_4H_9 (pKa = 2.5)

Procaine, R= H (pKa = 8.8)
Chloroprocaine, R=Cl (pKa = 9.0)
Propoxycaine, R=OC_3H_7 (pKa = 9.1)

Proparacaine (pKa = 9.1)

Tetracaine (pKa = 8.4)

Amino amides

Lidocaine (pKa = 7.8)

Prilocaine (pKa = 7.9)

Etidocaine (pKa = 7.7)

Mepivacaine, R= CH_3 (pKa = 7.6)
Bupivacaine, R= n-C_4H_9 (pKa = 8.1)

Ropivacaine, R= n-C_3H_7 (pKa = 8.2)
Levobupivacaine, R= n-C_4H_9 (pKa = 8.1)

Articaine (pKa = 7.8)

Dibucaine (pKa = 8.8)

Amino ethers

Pramoxine (pKa = 7.1)

Amino ketone

Dyclonine (pKa = 8.2)

Alcohols

Benzyl alcohol

Menthol

Phenols

Eugenol

Phenol

Therapeutic Considerations for Using Local Anesthetic Drugs

Table 16.9 contains chemical structures of the different types of agents in current or recent use.

TABLE 16.8 Clinically Available Local Anesthetics

Generic Name	Trade Name	Recommended Application
Articaine	Septocaine, Septanest	Parenteral (dental)
Benoxinate	Oxybuprocaine	Mainly in ophthalmology
Benzocaine	Americaine, Anbesol, Benzodent, Orajel, Oratect, Rid-A-Pain, Hurricaine	Topical
Benzyl alcohol		Topical, mainly in combination with pramoxine
Bupivacaine	Marcaine, Sensorcaine	Parenteral
Butamben	Butesin	Topical
Chloroprocaine	Nesacaine	Parenteral
Dibucaine	Nupercainal, Cinchocaine	Topical
Dyclonine	Sucrets	Topical (mucosal only)
Etidocaine	Duranest	Parenteral
Ethyl chloride		Extracutaneous, temperature decreasing
Eugenol		Topical, especially in dentistry
Levobupivacaine	Chirocaine	Parenteral
Lidocaine	Xylocaine, L-Caine, DermaFlex, Dilocaine, Lidoject, Lignocaine, Octocaine,	Parenteral, topical
Mepivacaine	Carbocaine, Polocaine, Isocaine	Parenteral, topical
Menthol	Chloraseptic lozenges, Dermoplast, Pramegel, Pontacaine ointment	Topical, mainly in combination with benzocaine or pramoxine or tetracaine
Phenol	Anbesol	Topical, mainly in combination with benzocaine
Pramoxine	Prax, Tronothane	Topical
Prilocaine	Citanest	Parenteral, topical
Procaine	Novocain	Parenteral
Proparacaine	Alcaine, Ophthaine, Ak-Taine	Mainly in ophthalmology
Propoxycaine	Blockaine, Ravocaine	Parenteral
Ropivacaine	Naropin	Parenteral
Tetracaine	Pontocaine, Amethocaine, Prax	Parenteral, topical

Articaine

all other amino amide–type local anesthetics in that it contains the bioisosteric thiophene ring instead of a benzene ring and a carbomethoxy group. This renders the molecule more lipophilic and, thus, makes it easier to cross lipoidal membranes. Its local anesthetic potency is approximately 1.5-fold that of lidocaine, even though it has similar pKa (7.8) and smaller log DpH 7.4 (1.65 vs. logDpH 7.4 of 2.26 for lidocaine) and plasma protein binding (76%) properties. Articaine is metabolized primarily by plasma cholinesterases because of the presence of an ester group and, therefore, has a much shorter duration of action than lidocaine (i.e., only approximately one-fourth that of lidocaine). Articaine undergoes rapid hydrolysis of the carbomethoxy group to give articainic acid, which is eliminated either unchanged (75%) or as its glucuronides (25%). Compared with other short-acting, amino amide–type local anesthetics, such as mepivacaine, lidocaine, or prilocaine, articaine is said to be a much safer drug for regional anesthesia and is the drug of choice for dental procedures.

Pharmaceutical Preparations

Local anesthetic agents generally are prepared in various dosage forms: aqueous solutions for parenteral injection, and creams and ointments for topical applications. Thus, chemical stability and aqueous solubility become primary factors in the preparations of suitable pharmaceutical dosage forms.

Metabolism of Local Anesthetics

An understanding of the metabolism of local anesthetics is important in clinical practice because the overall toxicity of a drug depends not only on its uptake and tissue distribution but also on how it is deactivated in vivo. The amino ester–type local anesthetics are rapidly hydrolyzed by plasma cholinesterase (also known as pseudocholinesterase), which is widely distributed in body tissues. These compounds can therefore be metabolized in the blood, kidneys, and liver and, to a lesser extent, at the site of administration. For example, both procaine and benzocaine are easily hydrolyzed by cholinesterase into PABA and the corresponding N,N′-diethylaminoethyl alcohol. It is not surprising that potential drug interactions exist between the amino ester–type local anesthetics and other clinically important drugs, such as cholinesterase inhibitors or atropine-like anticholinergic drugs. These compounds either inhibit or compete with local anesthetics for cholinesterases, therefore prolonging local anesthetic activity and/or toxicity. Another potential drug interaction with clinical signifi cance can be envisioned between benzocaine and sulfonamides; that is, the hydrolysis of benzocaine to PABA can antagonize the antibacterial activity of sulfonamides.

The amino amide–type local anesthetics, however, are metabolized primarily in the liver, involving CYP1A2 isozymes. A general metabolic scheme for lidocaine is shown in **Figure 16.17**.

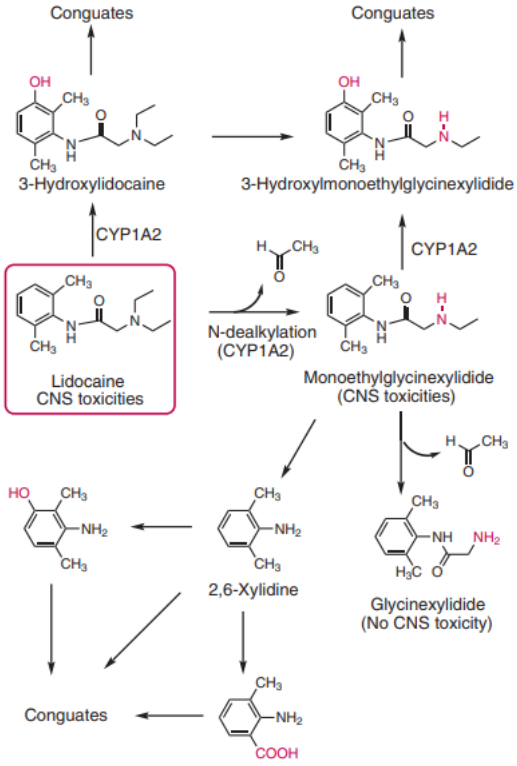

FIGURE 16.17 Metabolic scheme for lidocaine.

Common Agents Used for Local Anesthesia

Local anesthetics are widely used in many primary care settings. Techniques for their administration in these settings include topical application, local infi ltration, fi eld block, and peripheral nerve block. Their use can be maximized by an understanding of their potencies, durations of action, routes of administration, and pharmacokinetic and side effect profi les. The generic name, trade name, and recommended application are given in Table 16.8, and the chemical structures of these agents can be found in **Table 16.9**.

Onset and duration of action

The onset and duration of action of local anesthetics are influenced by several factors including tissue pH, nerve morphology, concentration, pKa, and lipid solubility of the drug. Of these, the pH of the tissue and pKa are the most important. At physiologic pH, these compounds are charged. 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. Within limits, higher concentration and greater lipid solubility improve onset somewhat. Duration of action depends on the length of time the drug can stay near the nerve to block sodium channels.

Actions

• Local anesthetics cause vasodilation, leading to rapid diffusion away from the site of action and shorter 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, which is determined by redistribution and not biotransformation.

• Some local anesthetics have other therapeutic uses (for example, lidocaine is an IV antiarrhythmic).

Administration to children and the elderly

• Before administering local anesthetic to a child, the maximum dose based on weight should be calculated to prevent accidental overdose.

• There are no significant differences in response to local anesthetics between younger and older adults.

• It is prudent to stay well below maximum recommended doses in elderly patients who often have some compromise in liver function.

• Because some degree of cardiovascular compromise may be expected in elderly patients, reducing the dose of epinephrine may be prudent.

• Local anesthetics are safe for patients who are susceptible to malignant hyperthermia.

Systemic local anesthetic toxicity

• Toxic blood levels of the drug may be due to repeated injections or could result from a single inadvertent IV injection.

• Aspiration before every injection is imperative. The signs, symptoms, and timing of local anesthetic systemic toxicity are unpredictable. One must consider the diagnosis in any patient with altered mental status or cardiovascular instability following injection of local anesthetic. CNS symptoms may be apparent but may also be nonspecific or absent.

• Treatment for systemic local anesthetic toxicity includes airway management, support of breathing and circulation, seizure suppression and, if needed, cardiopulmonary resuscitation. Administering a 20% lipid emulsion infusion (lipid rescue therapy) is a valuable asset.

CHARACTERISTIC	ESTERS • *Procaine* • *Tetracaine* • *Chloroprocaine* • *Cocaine*	AMIDES • *Lidocaine* • *Mepivacaine* • *Bupivacaine* • *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
pK_a's	Higher than physiologic pH (8.5–8.9)	Close to physiologic pH (7.6–8.1)

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

Figure 6: Summary of pharmacologic properties of some local anesthetics. PABA = para-aminobenzoic acid. (MEMORISABLE)

Refrence:

1- TIMOTHY J. MAHER. "***Anesthetic Agents: General and Local Anesthetics***". Chapter 16.

2- Whalen, Karen. "Lippincott® ***illustrated reviews: pharmacology***". Wolters kluwer india Pvt Ltd, 2018.

References:

1- Katzung, B.G., 2018. Basic and clinical pharmacology. Mc Graw Hill.
2- Whalen, K., 2019. Lippincott illustrated reviews: pharmacology. Lippincott Williams & Wilkins.
3- https://dimensionsofdentalhygiene.com/article/the-complexity-of-addiction/