Anesthetics

CAROLYN J. FRIEL

CHAPTER OVERVIEW

This chapter focuses on the general and local anesthetic drugs used to block the transmission of pain. The general anesthetic section covers both the inhaled and the intravenous drugs. The local anesthetic section includes the topical and parenteral drugs. This chapter includes the mechanism of action, structure–activity relationships (SAR), and individual drug monographs for the general and the local anesthetic agents.

THE INHALED GENERAL ANESTHETICS

In 1846, a Boston dentist, William Morton, demonstrated the use of ether as a general anesthetic in a public demonstration. The publication of the successful operation led to the use of general anesthetics by surgeons and ushered in the "age of anesthesia." The first paper that described the use of the general anesthetic ended with the warning that "Its action is not yet thoroughly understood, and its use should be restricted to responsible persons."[1] Although it has been 160 years since that statement was written, the sentiment remains today.

The pharmacological mechanism of action of the anesthetic drugs is not clear. The idea that we can understand the mechanism of action for a general anesthetic supposes that we understand what the term anesthesia means. A clinical definition of general anesthesia is a state where no movement occurs in response to what should be painful. Although this gives us a working definition of the drug's action, it does not explain the physiology behind the action. Much research remains to be done on the physiological mechanism of action of the drugs discussed in this chapter. The general anesthetic section will begin by reviewing the stages of general anesthesia, followed by a summary of the SAR of the inhaled anesthetics and their proposed mechanism of action and will conclude with individual drug monographs.

Stages of General Anesthesia[2]

Analgesia (Stage I): The stage of analgesia lasts from onset of drowsiness to loss of eyelash reflex (blinking when the eyelash is stroked). Variable levels of amnesia and analgesia are seen in this stage. The patient is considered unconscious at the end of stage I.

Excitement (Stage II): The stage of excitement is characterized by agitation and delirium. During this stage, salivation may be copious. Heart rate and respiration may be irregular. Induction agents are designed to move the patient through this undesirable stage quickly.

Surgical Anesthesia (Stage III): This stage is divided into four planes but for the purpose of this chapter, it is sufficient to understand that this stage of anesthesia is the target depth for the procedure. During this stage, a painful stimuli will not elicit a somatic reflex or deleterious autonomic response.

Impending Death (Stage IV): This stage lasts from onset of apnea to failure of circulation and respiration and ends in death.

The ideal anesthetic combination will allow the patient to proceed quickly from stage I to stage III and avoid stage IV. Inhaled anesthetics are used in combination with other drugs to induce anesthesia. The drug combinations used to achieve this are complex and will not be addressed here; the reader is referred to a general anesthesia textbook for a more detailed description.

The Ideal Inhaled Anesthetic

The ideal inhaled anesthetic will be inexpensive, potent, pleasant to inhale, minimally soluble in the blood and tissues, stable on the shelf and during administration, and lack undesirable side effects such as cardiotoxicity, hepatotoxicity, renal toxicity, and neurotoxicity. The ideal inhaled anesthetic has not been developed yet and all of these factors must be kept in mind when choosing an anesthetic for a particular patient.

POTENCY

The most common way to measure inhaled anesthetic potency is by recording the minimum alveolar concentration (MAC) needed to prevent movement to a painful stimulus. The MAC concentrations are recorded at 1 atmosphere and reported as the mean concentration needed to abolish movement in 50% of subjects. The MACs for the inhaled anesthetics are listed in Table 22.1. Potency of the inhaled anesthetics is extremely important as the anesthetic gas is displacing oxygen in the inspired gas. Inhaled agents with low potencies (high MACs) such as nitrous oxide require administration at increased pressure or are used only in combination with more potent inhaled agents.

SOLUBILITY

The ideal general anesthetic will have low solubility in blood conveyed by the blood:gas partition coefficient listed

TABLE 22.1 Properties of the Inhaled Anesthetics

Anesthetic	MAC (%)	Blood:Gas	Oil:Gas
Nitrous oxide	104	0.46	1.1
Halothane	0.75	2.4	137
Enflurane	1.68	1.8	98
Methoxyflurane	0.16	16.0	970
Isoflurane	1.15	1.43	90.8
Sevoflurane	2.10	0.65	50
Desflurane	7.3	0.42	18.7
Xenon	71	0.12	1.9

in Table 22.1. The blood:gas partition coefficient is defined as the ratio of the concentration of the drug in the blood to the concentration of the drug in the gas phase (in the lung), at equilibrium. The volatile anesthetic is inhaled into the lungs, diffuses into the blood, and when equilibrium is reached, it diffuses into tissues. For the drug to have a quick onset, the solubility in the blood should be low, thus saturation will occur quickly, and the drug can then move into the tissue compartment. Recovery is also expected to be faster for those drugs with a low blood:gas partition coefficient as the drug will be eliminated quicker if it has a low solubility in the blood and quickly passes into the lungs for exhalation.

When a patient is exposed to the volatile gas for prolonged procedures, greater than 5 hours, the solubility of the drug in the tissues will also effect the recovery period. In these cases, it is necessary to consider the solubility of the drug in fat and lean organs as well as the body mass of the individual patient to determine how recovery could be affected by drug solubility. Most inhaled anesthetics have similar solubilities in lean organs, but their solubilities in fat vary as predicted by their oil:gas partition coefficients listed in Table 22.1.[3] Obese patients may have increased recovery times if an inhaled anesthetics with high-fat solubility is used for a prolonged period.

STABILITY

The early inhaled anesthetics suffered from stability problems, leading to explosions and operating room fires. By halogenating the ether and hydrocarbon anesthetics, the explosiveness and flammability of the drugs were diminished, and the number of operating room fires decreased. Halogenation clearly stabilizes the inhaled agent and all inhaled anesthetics used today contain halogens.

Sporadic reports of fires involving sevoflurane can be found in the literature.[4–6] The operating room fires involving sevoflurane all involved the recapture process and recirculating equipment. In an attempt to decrease operating room personnel exposure to the volatile anesthetics being exhaled by the patient, as well as to reduce the acquisition costs of the drug, recirculating breathing apparatus were developed. These breathing apparatus are designed to capture the expired gas, remove the carbon dioxide, and then allow the patient to inhale the anesthetic gas again. Different carbon dioxide absorbents are used such as calcium hydroxide, barium hydroxide, and sodium hydroxide. When the absorbent inadvertently dries out, as a result of the continuous flow of fresh gas, sevoflurane can break down and produce hydrogen in an exothermic reaction. The generation of hydrogen and heat may have been responsible for the reported fires that began in the anesthetic equipment.[6] Other anesthetics have not had this same problem but all are monitored for their degradation products when exposed to carbon dioxide absorbents. Toxic metabolites of the inhaled anesthetics, such as the fluoride anion, are also a concern and discussed in the individual drug monographs.

Structure–Activity Relationships of the Volatile General Anesthetics

The inhalation anesthetics in use today are nitrous oxide, halothane, isoflurane, desflurane, and sevoflurane. The chemical structures for these compounds and some of historical interest can be seen in Figure 22.1. While it is true that there is no single pharmacophore for the inhaled anesthetics, the chemical structure is related to the activity of the drug molecule.

ALKANE/CYCLOALKANE

alkane series   cycloalkane series
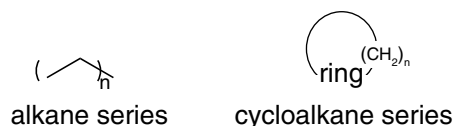
The first SAR studies conducted independently by Meyer and Overton in the 1880s showed a distinct positive correlation between anesthetic potency and solubility in olive oil. Many series of compounds confirm this simple relationship but exceptions to the model exist. The potency of alkanes, cycloalkanes, and aromatic hydrocarbons increases in direct proportion to the number of carbon atoms in the structure up to a cutoff point.[7] Within the n-alkane series, the cutoff number is 10, with n-decane showing minimal anesthetic potency. In the cycloalkane series, the cutoff number in most studies is eight with cyclooctane showing no anesthetic activity in the rat. The reduced activity of the compounds beyond their cutoff number could be a result of problems getting to the site of action (reduced vapor pressure or high blood solubility) or inability to bind to the site of action and induce the conformational change required for anesthetic action.[8]
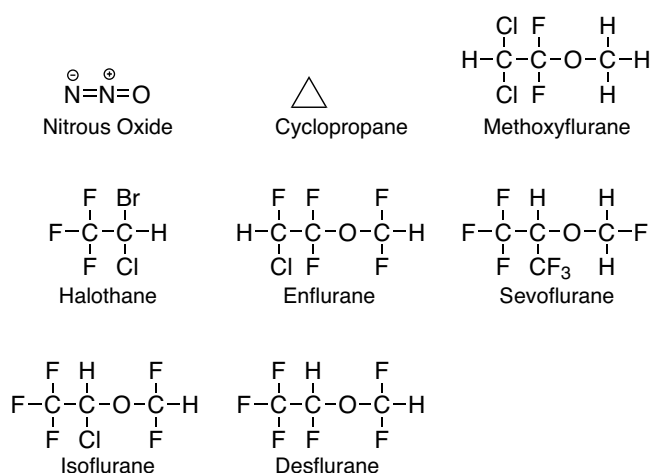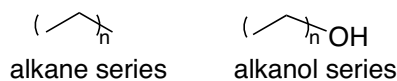

Figure 22.1 ● The chemical structures of the inhaled anesthetic agents.

The cycloalkanes are more potent anesthetics than the straight chain analog with the same number of carbons. For example, the MAC of cyclopropane in rats is about one fifth of the MAC of n-propane.[8]

ALKANOL SERIES

alkane series   alkanol series

A similar increase in potency with increase in carbon length was seen in the n-alkanol series. In addition, the n-alkanol with a given number of carbons is more potent than the n-alkane with the same chain length.[9]

EFFECT OF HALOGENATION/ETHER HALOGENATION

The first inhaled anesthetics used in the late 1800s, diethyl ether and cyclopropane caused laryngospasms. These compounds were also explosive and flammable requiring careful handling. Early studies found that halogenating the ethers decreased the flammability of the compounds, enhanced their stability and increased their potency. Higher atomic mass halogens increased potency compared to lower atomic mass halogens. For example, replacing the fluorine in desflurane ($CF_2HOCFHCF_3$) with a chlorine to form isoflurane ($CF_2HOCClHCF_3$) increased potency more than fourfold.[10] Replacing the chlorine with bromine in the investigational agent I-537 ($CF_2HOCBrHCF_3$) increased potency threefold further. In general, halogenated ether compounds also caused less laryngospasms than unhalogenated compounds. Unfortunately, halogenation also increased the propensity of the drugs to cause cardiac arrhythmias and/or convulsions.[11] Halogenated methyl ethyl ethers were found to be more stable and potent than halogenated diethyl ethers. The commonly used inhaled anesthetics are ethers or aliphatic hydrocarbons with 2 to 5 carbon atoms.

The effect of halogenating the alkane, cycloalkane, and alkanol compounds has been extensively studied in animal models. For the n-alkane series, fully saturating the alkane with fluorine abolished activity except when n equaled one.[7] When n was 2 to 4 carbons the highest potency was seen when the terminal carbon contained one hydrogen ($CHF_2(CF_2)_nCHF_2$). When n was greater than 5 carbons the potency decreased in this series. The potency of the dihydrogen compounds ($CH_2F(CF)_nCH_2F$) (n = 2–4) was greater than the equivalent nonfluorinated alkane compound. Similar findings for the n-alkanol series were found. The most potent fluorinated n-alkanols were the $CHF_2(CF_2)_nCH_2OH$ series, when n was between 2 and 5.[7] The decrease in activity for the completely fluorinated compounds would not be predicted by the Meyer-Overton hypothesis. Another interesting phenomenon that does not follow the Meyer-Overton hypothesis can be found using the structural isomers isoflurane and enflurane. (Fig. 22.1) The compounds have similar solubility in oil, yet the MAC for enflurane is greater than the MAC for isoflurane (Table 22.1). The stereoisomers of isoflurane (+) and (−) have also been isolated and tested for anesthetic potency in rats. The (+) isomer was found to be 53% more potent than the (−) isomer. This observation would not be predicted based on the Meyer-Overton hypothesis.

EFFECT OF SATURATION

Molecular flexibility of the inhaled anesthetics is not required. The addition of double and/or triple bonds to small anesthetic molecules having 6 carbon atoms or less increases potency.[12]

Mechanism of Action of the Inhaled Anesthetics

The mechanism of action of the inhaled anesthetics is not known. Most theories of the inhaled anesthetics leave room for the possibility of multiple mechanisms, receptors, and regions of the nervous system (spinal cord and brain) to explain their action. It seems likely that the individual anesthetic molecules act with different potencies on multiple receptors that lead to similar clinical states of anesthesia. Some of theories of anesthetic action are briefly covered below.

MEYER-OVERTON THEORY

As discussed, work of Meyer and Overton in the 1880s showed that there was strong correlation between the potency of the anesthetic and its solubility in olive oil. This correlation holds true for a surprising number of inhaled anesthetics but it does not explain the drugs mechanism of action. When biological membranes were found to be composed mainly of lipids, the work of Meyer and Overton was extended to offer a proposed mechanism of action of the inhaled anesthetics. Namely, that the lipid-soluble drug somehow disrupted the biological membrane and produced anesthesia. This "unitary hypothesis" has led to research focused on the effect of the anesthetics on the lipid membrane. The inhaled anesthetics do disrupt the lipid bilayer but it is unclear if they make enough changes to effect cell signaling.[13] If lipid solubility were the only factor for anesthetic potency, then chiral enantiomers would have the same potencies as their log P's are identical. This is not the case. The stereoisomers of isoflurane do not have the same in vivo potency (~20%) despite having the same effect on the lipid membrane.[13] It is also clear that all lipophilic chemicals are not anesthetics and thus the unitary theory of anesthesia cannot adequately explain the mechanism of action of the inhaled anesthetic drugs.

INTERACTION WITH ION CHANNELS[14]

Inhaled anesthetics interact with various ion channels to influence the electrical activity of cells and their physiological response. The most studied receptor that inhaled anesthetics act on is the $GABA_A$ receptor. Inhaled anesthetics enhance chloride ion conductance into the cell and thus hyperpolarize the cell membrane and prevent impulse transmission. They act at the $GABA_A$ receptor in a manner similar to the benzodiazepines but not identical. Molecular modeling studies based on mutagenesis data and structurally homologous proteins predict the existence of an inhaled anesthetic binding site on the $GABA_A$ receptor. The binding site is postulated to be between the second and third transmembrane segments of the $GABA_A$ α_1-receptor subunits.[15] Chloride channel blockers and benzodiazepine antagonists show only a small effect on the potency of the anesthetics, thus $GABA_A$ potentiation cannot universally explain their mechanism of action.[13] Inhaled anesthetics are also known

to enhance the major inhibitory receptors in the spinal cord, the glycine receptors.

Inhaled anesthetics are also proposed to inhibit the excitatory synaptic channel activity of neuronal nicotinic acetylcholine receptors, glutamate receptors (*N*-methyl-D-aspartate [NMDA] and *α*-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid [AMPA]), sodium channels, potassium channels, calcium channels (voltage-gated cardiac and neuronal), and ryanodine receptors. The multitude of receptor channels that are affected to various degrees by specific inhaled anesthetics leads to the current theory that multiple receptors are targets of the volatile anesthetics and no single receptor–drug interaction can fully explain their mechanism of action.

General Anesthetic Monographs, Individual Products Including Adverse Reactions

The chemical structures of the inhaled anesthetic agents are shown in Figure 22.1.

NITROUS OXIDE

Nitrous oxide is a gas at room temperature and is supplied as a liquid under pressure in metal cylinders. Nitrous oxide is a "dissociative anesthetic" and causes slight euphoria and hallucinations. The low potency of nitrous oxide (MAC = 104%) precludes it from being used alone for surgical anesthesia. To use it as the sole anesthetic agent the patient would have to breathe in pure N_2O to the exclusion of oxygen. This situation would obviously cause hypoxia and potentially lead to death. Nitrous oxide can inactivate methionine synthase, a B_{12}-dependent enzyme necessary for the synthesis of DNA and therefore should be used with caution in pregnant and B_{12}-deficient patients. Nitrous oxide is also soluble in closed gas containing body spaces and can cause these spaces to enlarge when administered possibly leading to adverse occurrences (occluded middle ear, bowel distension, pneumothorax). Nitrous oxide is a popular anesthetic in dentistry were it is commonly referred to as "laughing gas." It is used in combination with more potent anesthetics for surgical anesthesia and remains a drug of recreational abuse.[16] Nitrous oxide undergoes little or no metabolism.[3]

HALOTHANE

Halothane is a nonflammable, nonpungent, volatile, liquid, halogenated (F, Cl, and Br) ethane (bp = 50°C), introduced in 1956. Halothane may increase heart rate, cause cardiac arrhythmias, increase cerebral blood flow, and increase intracranial pressure.[17] It can undergo spontaneous oxidation when exposed to ultraviolet light to yield HCl, HBr, Cl^-, Br^-, and phosgene ($COCl_2$). To prevent oxidation it is packaged in amber bottles with a low concentration of thymol (0.01%) as a stabilizer. The drug has a high potency (MAC = 0.75%), a blood:gas partition coefficient of 2.4, and high adipose solubility. Halothane undergoes both reductive and oxidative processes with up to 20% of the dose undergoing metabolism (Fig. 22.2).[18] The trifluoroacetyl chloride metabolite is electrophilic and can form covalent bonds with proteins leading to immune responses and halothane hepatitis upon subsequent halothane exposure. Halothane hepatitis is rare with 1 case reported for every 6,000 to 35,000 patients exposed.[17,18]

The use of inhaled anesthetics and halothane in particular can produce malignant hyperthermia (MH) in genetically susceptible individuals. This results in an increase in body temperature, tachycardia, tachypnea, acidosis, and rhabdomyolysis. MH is a result of the excessive release of calcium from the sarcoplasmic reticulum (SR). Patients with an inherited mutation in the ryanodine receptor (RYR1), which is located in the SR, are at an increased risk of developing MH when exposed to an inhaled anesthetic triggering agent. Treatment entails discontinuing the anesthetic agent, rapid cooling, intravenous dantrolene sodium, and supportive measures. MH has been reported to occur with all anesthetics agents and with succinylcholine, a depolarizing neuromuscular blocker. The combination of halothane and succinylcholine appears to trigger a great extent of the MH episodes. Patients with a family history of MH can be genetically screened for MH susceptibility via the caffeine–halothane contracture test. This test is invasive requiring a piece of skeletal muscle to conduct and it is expensive costing approximately $5,000 (cost in 2008). Noninvasive molecular genetic screening is currently being developed.[19]
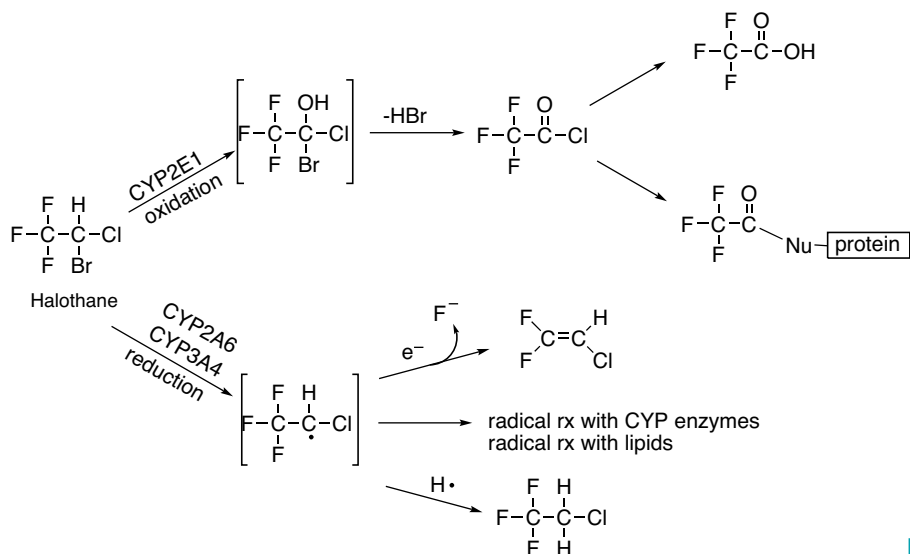

Figure 22.2 ● Halothane metabolism.

METHOXYFLURANE

Methoxyflurane is a volatile liquid (bp = 105°C) with a high blood:gas partition coefficient and thus a slow induction and prolonged recovery.[20] Approximately 75% of the drug undergoes metabolism yielding dichloroacetate, difluoromethoxyacetate, oxalate, and fluoride ions. The intrarenal inorganic fluoride concentration, as a result of renal defluorination, may be responsible for the nephrotoxicity seen with methoxyflurane. Both the concentration of F^- generated and the duration for which it remained elevated were factors in the development of methoxyflurane nephrotoxicity.[21] Methoxyflurane was removed from the U.S. market in 2000 because of safer alternatives. Both isoflurane and enflurane produce less fluoride ion upon metabolism than methoxyflurane.

ENFLURANE

Enflurane is a volatile liquid (bp = 56.5°C) with a blood:gas partition coefficient of 1.8 and an MAC of 1.68%. Approximately 2% to 8% of the drug is metabolized primarily at the chlorofluoromethyl carbon. Little chlorofluoroacetic acid is produced suggesting minor metabolism at the difluoromethyl carbon. Difluoromethoxydifluoroacetate and fluoride ion have been reported as metabolites. Enflurane may increase heart rate, cause cardiac arrhythmias, increase cerebral blood flow, and increase intracranial pressure but all to a smaller degree than halothane.[17] Enflurane also causes electroencephalographic (EEG) patterns consistent with electrical seizure activity. It has caused tonic–clonic convulsive activity in patients when used at high concentrations or during profound hypocarbic periods. Enflurane is therefore not recommended in patients with seizure disorders.[22]

ISOFLURANE

Isoflurane is a volatile liquid (bp = 48.5°C) with an MAC of 1.15, a blood:gas partition coefficient of 1.43 and high solubility in fat. Isoflurane is a structural isomer of enflurane. It is a known respiratory irritant, but less so than desflurane. Approximately 0.2% of the administered drug undergoes metabolism, the rest is exhaled unchanged. The metabolism of isoflurane yields low levels of the nephrotoxic fluoride ion as well as a potentially hepatotoxic trifluoroacetylating compound (Fig. 22.3).[23] The relatively low concentrations of these compounds have resulted in very low risks of hepatotoxicity and nephrotoxicity. There have been no reports of

seizures caused by isoflurane and only transient increases in heart rate have been reported.

DESFLURANE

Desflurane is a nonflammable, colorless, very volatile liquid packaged in amber-colored vials. The boiling point is 22.8°C, and it requires a vaporizer specifically designed for desflurane. The manufacturer states that the vials can be stored at room temperature. Desflurane has a blood:gas partition coefficient of 0.42, an MAC of 7.3% and an oil:gas partition coefficient of 18.7. The low blood:gas partition coefficient leads to fast induction times and short recovery times. Desflurane is not recommended for induction anesthesia in children because of the high incidence of laryngospasms (50%), coughing (72%), breath holding (68%), and increase in secretions (21%).[24] Desflurane can produce a dose-dependent decrease in blood pressure and concentrations exceeding 1 MAC may cause transient increases in heart rate. Desflurane can react with desiccated carbon dioxide absorbents to produce carbon monoxide that may result in elevated levels of carboxyhemoglobin.[24]

Desflurane is metabolized minimally with less than 0.02% of the administered dose recovered as urinary metabolites. Desflurane produces minimal free fluoride ion and very little trifluoroacetic acid and has not been reported to cause either kidney or liver damage.

SEVOFLURANE

Sevoflurane is a volatile, nonpungent, nonflammable, and nonexplosive liquid with a boiling point of 58.6°C. The blood:gas partition coefficient is 0.65, the oil:gas partition coefficient is 50, and the MAC is 2.1%. Sevoflurane reacts with desiccated carbon dioxide adsorbents, to produce compounds (A and B) with known toxicity (Fig. 22.4). The type of CO_2 absorbent used, the temperature of the absorbent, and the duration of exposure can influence the degree to which sevoflurane breaks down.[25] The major breakdown product, compound A, pentafluoroisopropenyl fluoromethyl ether, (PIFE, $C_4H_2F_6O$) has been studied extensively.[25] Compound A is nephrotoxic in rats and nonhuman primates and remains a theoretical risk to humans.[26–28] As discussed previously under the stability of inhaled anesthetics, sevoflurane breakdown by CO_2 absorbents generates heat and has resulted in sporadic operating room fires.[5,29]
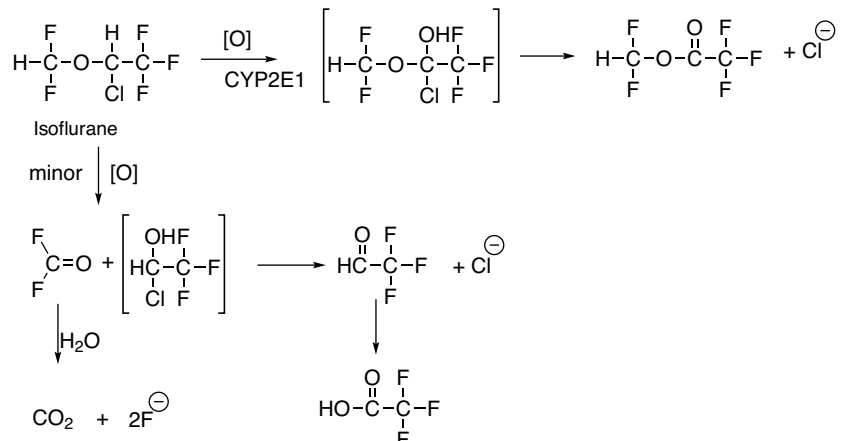

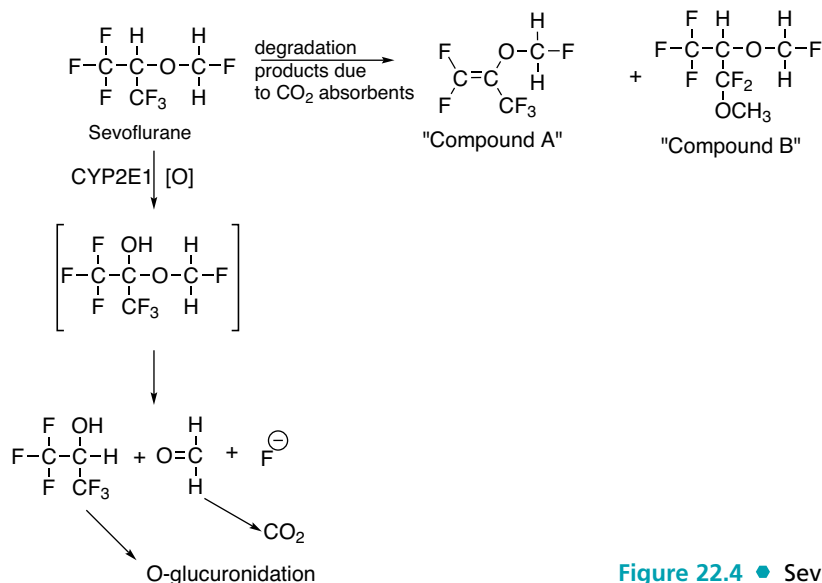**Figure 22.3** ◆ Isoflurane metabolism.

Figure 22.4 ● Sevoflurane metabolism and chemical instability.

Approximately 5% to 8% of the administered dose of sevoflurane is metabolized in man by CYP2E1 to hexafluoroisopropanol, CO_2 and the potentially nephrotoxic fluoride ion. (Fig. 22.4).[27,30,31] Patients should be monitored for increases in blood urea nitrogen (BUN) and creatine levels as high fluoride ion levels, and concerns about Compound A exposure, may induce renal toxicity. Sevoflurane has been studied in a small number of patients with preexisting renal insufficiency (creatine >1.5 mg/dL). Creatinine levels increased in 7% of renally impaired patients and the manufacturer recommends that it be used with caution in this patient population.[32] To reduce the potential toxicity in humans the use of sevoflurane should be limited to less than 2 MAC hours.[17]

Sevoflurane has been shown to cause epileptic changes on EEGs and case reports of seizures during surgery, especially in children, have been reported.[33]

XENON

Xenon is an inert gas that is nonflammable and nonexplosive. The outer shell of xenon is complete thus it is not a highly reactive compound neither seeking, nor donating electrons to biological molecules. Despite its "inert" status, xenon has been shown to interact with biological molecules by forming an induced dipole in the presence of a cationic site.[34] An induced dipole could also result from an interaction with another fleeting dipole formed at the proposed binding site to form an induced dipole-induced dipole or London dispersion force.[35] The mechanism of xenon anesthesia and the site of action are still unknown.

The low blood:gas partition coefficient (0.12) leads to quick onset and recovery, but the potency is low with an MAC of 71%. Xenon gas is produced in low quantities and presently is expensive to obtain. The low incidence of reported side effects, lack of environmental concerns (it will not contribute to the destruction of the ozone layer), and absence of metabolites makes xenon an interesting anesthetic for development.[36,37] Xenon is being tested in Japan and Europe presently and if a closed system anesthetic circulator is developed that can recapture the exhaled xenon the fiscal concerns may lesson. Patents have been awarded in the United States for xenon anesthetic equipment.

THE INJECTABLE GENERAL ANESTHETICS

General anesthesia includes the use of the inhalation anesthetics covered previously in this chapter and many intravenous drugs used during surgical procedures. The reader is referred to other chapters in this textbook for information on the benzodiazepines (Chapter 12), the barbiturates (Chapter 12), and the neuromuscular blockers (Chapter 17). Three additional drugs will be covered here that are solely used for their anesthetic effects: propofol, etomidate, and ketamine.

Propofol
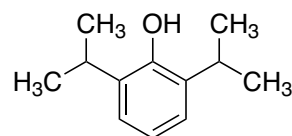
Propofol

Propofol is an injectable sedative–hypnotic used for the induction and maintenance of anesthesia or sedation. Propofol is only slightly soluble in water with an octanol/water partition coefficient of 6,761:1; thus, it is formulated as an oil-in-water emulsion. The fat component of the emulsion consists of soybean oil, glycerol, and egg lecithin. The pK_a of the propanol hydroxyl is 11 and the injectable emulsion has a pH of 7 to 8.5. Formulations contain either disodium ethylenediaminetetraacetic acid (EDTA) (0.005%) or sodium metabisulfite to retard the growth of microorganisms. EDTA is a metal chelator and patients on propofol containing EDTA for extended periods of time excrete more zinc and iron in their urine.[38] The clinical consequence of this is not known but the manufacturer recommends that a drug holiday or zinc supplementation be considered after 5 days of therapy.[39] Generic formulations of propofol may contain sodium metabisulfite as the antimicrobial agent, and patients allergic to sulfites, especially asthmatic patients, should avoid this formulation.[40] Aseptic technique must be followed and unused portions of the drug must be discarded according to the
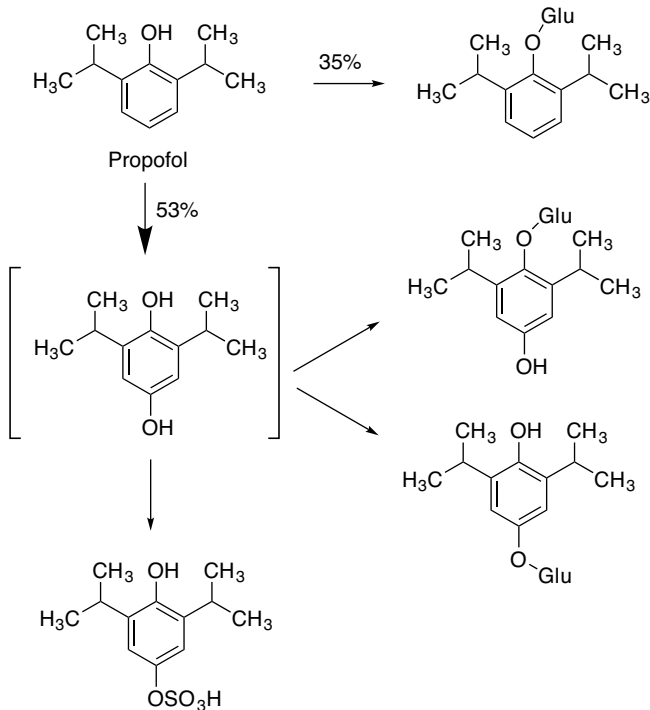
Figure 22.5 ● Metabolism of propofol.

manufacturer's instructions to prevent microbial contamination and possible sepsis.

Although unrelated chemically to the inhaled anesthetics, propofol has been shown to be a positive modulator of the $GABA_A$ receptor. The binding site on $GABA_A$ is distinct from the benzodiazepine binding site, and propofol binding is not inhibited by the benzodiazepine antagonist flumazenil.[41] The propofol binding site is believed to be on the β subunit. Propofol also directly activates Cl currents at glycine receptors, the predominant spinal inhibitory receptor. Unlike many volatile general anesthetics, propofol does not enhance the function of serotonin 5-HT$_3$ receptors and this may explain its low incidence of postoperative nausea and vomiting.[42] Propofol shows no analgesic properties, but it does not increase sensitivity to pain like some barbiturates.[43] Propofol causes a dose-dependent decrease in blood pressure and heart rate and a threefold to fourfold increase in serum triglyceride concentrations after 7 days of administration.[40]

Propofol is quickly and extensively metabolized with 88% of a ^{14}C-labelled intravenous administered dose appearing in the urine as conjugates. Less than 2% of the dose is found unchanged in the feces and less than 0.3% found unchanged in the urine (Fig 22.5). Thirty minutes after the ^{14}C-labelled dose was administered, 81% of the radioactivity was in the form of metabolites.[43] Propofol has a quick onset of action (arm-to-brain circulation time) and a quick recovery time.

Etomidate
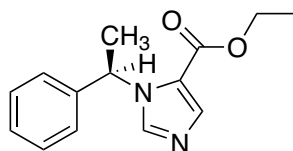
Etomidate

Etomidate is a carboxylated imidazole intended for the induction of general anesthesia. It is marketed as the more potent R (+) isomer. It is believed to exert its anesthetic effect via positive modulation of the $GABA_A$ receptor.[44] It is not water soluble and is available in the United States as a 2-mg/mL solution containing 35% v/v propylene glycol and in Europe as a soybean oil and medium-chain triglycerides formulation.[45,46] The propylene glycol has been associated with moderate-to-severe pain on injection and irritation of the vascular tissue.[46] A high incidence of skeletal muscle movements were noted in about 32% of patients following etomidate injection. Case reports of seizures are also found in the literature.[47] Administration of etomidate has little effect on cardiac output, peripheral, or pulmonary circulation. Studies have found that etomidate, even after a single dose, reduces plasma cortisol and aldosterone levels. Etomidate should not be used in patients with severe sepsis as the adrenal insufficiency has been shown to increase the risk of death in these patients.[48] This is probably a result of the inhibition of the 11 β-hydroxylase enzyme. Etomidate should only be used for induction of anesthesia when the cardiac benefits outweigh the risks associated with adrenal insufficiency.

Etomidate is quickly distributed throughout most organs in the body after intravenous administration and the tissue concentrations equal and sometimes exceed the plasma concentrations. The lipid solubility of the drug allows it to rapidly penetrate into the brain with peak concentrations occurring within 1 minute of administration. Etomidate is rapidly metabolized in the plasma and liver via esterases. About 75% of the drug is eliminated in the urine as the inactive ester hydrolyzed carboxylic acid.[49]

Ketamine
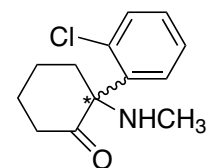
Ketamine

Ketamine is formulated as an acidic solution, pH 3.5 to 5.5, available with or without 0.1 mg/mL benzethonium chloride preservative. Ketamine is marketed as the racemic mixture and some properties of the individual isomers have been elucidated.[50] Ketamine is a rapid-acting agent that can be used for induction, used as the sole agent for general anesthesia or combined with other agents. Unlike the proposed mechanism of action for most anesthetics, ketamine does not act at the $GABA_A$ receptor. Ketamine acts as a noncompetitive antagonist at the glutamate, NMDA receptor, a nonspecific ion channel receptor. The NMDA receptor is located throughout the brain and contains four well-studied binding sites. The primary binding site binds L-glutamate, NMDA, and aspartate. The allosteric site binds glycine, which facilitates primary ligand binding. There is also a magnesium binding site that blocks ion flow through the channel and a phencyclidine (PCP) binding site that blocks the ion channel when occupied. Ketamine is believed to bind to the PCP site in a stereoselective manner and block the ion flow in the channel.[51] By blocking the flow of calcium ions into the cell, ketamine prevents the calcium
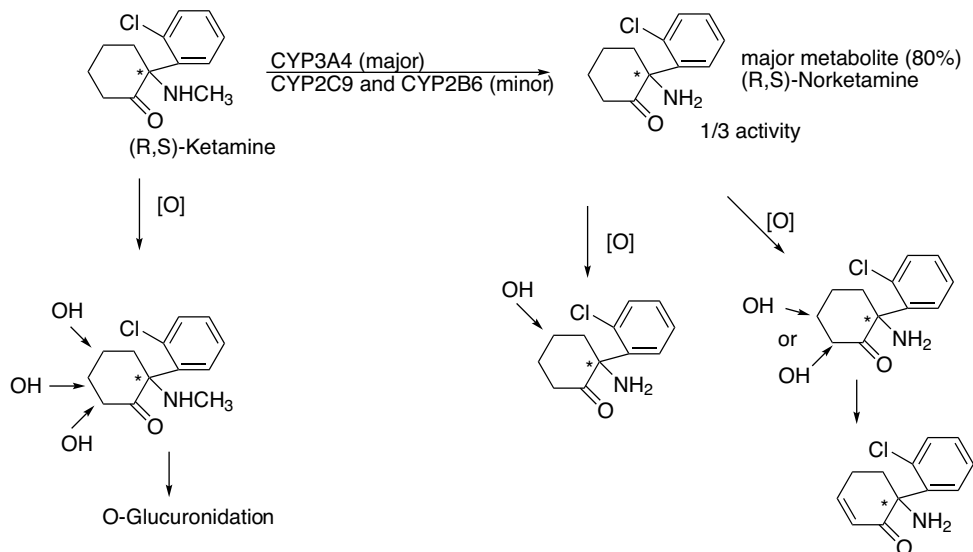
Figure 22.6 ● Metabolism of ketamine.

concentration from building and triggering excitatory synaptic transmissions in the brain and spinal cord.

Ketamine causes a transient increase in blood pressure after administration and is contraindicated in patients whom a significant elevation of blood pressure would constitute a serious hazard. Ketamine has also been found to bind to mu, delta, and kappa opioid receptors as well as the sigma receptors. The $S(+)$ ketamine is two to three times more potent than the $R(-)$ ketamine as an analgesic.[51] Ketamine has different effects at different doses on the opioid receptors and the use of ketamine as a postoperative analgesic or for chronic pain requires more study.[52,53]

Ketamine is classified as a "dissociative anesthetic," and psychological manifestations during emergence of anesthesia occur in 12% of patients. These vary from pleasant dreamlike states to vivid hallucinations and delirium. The duration is usually for only a few hours but patients have reported recurrences taking place up to 24 hours postoperatively. The incidence of this appears to be less in children younger than 16 years of age and in patients older than 65 years of age. Like other dissociative anesthetics, ketamine is abused for its hallucinatory effects. Most of the illegally used ketamine comes from stolen legitimate sources, particularly from veterinary clinics or smuggled in from Mexico.[54]

Ketamine is metabolized via *N*-demethylation to form the main metabolite norketamine. Norketamine has about one third the potency of the parent compound. Minor metabolic pathways include hydroxylation of the cyclohexanone ring; hydroxylation followed by glucuronide conjugation, and hydroxylation followed by dehydration to the cyclohexenone derivative (Fig. 22.6).[55,56]

THE LOCAL ANESTHETICS

Drugs classified as local anesthetics inhibit the conduction of action potentials in all afferent and efferent nerve fibers. Thus, pain and other sensations are not transmitted effectively to the brain, and motor impulses are not transmitted effectively to muscles. Local anesthetics have various clinical uses to treat acute or chronic pain or to prevent the sensation of pain during procedures. To understand the mechanism of action of the local anesthetics, an introduction to the physiology of nerve fibers and the transmission of pain sensation is briefly discussed below.

Physiology of Nerve Fibers and Neurotransmission

The nervous system functions to receive stimulation and transmit stimulus via the nerve cells or neurons. A neuron is a single cell typically composed of a cell body connected via an axon to the axon terminal (Fig. 22.7). The axon terminal is the presynaptic component of the nerve synapse and may contain neurotransmitters ready to be released upon receiving an action potential "message". The axon
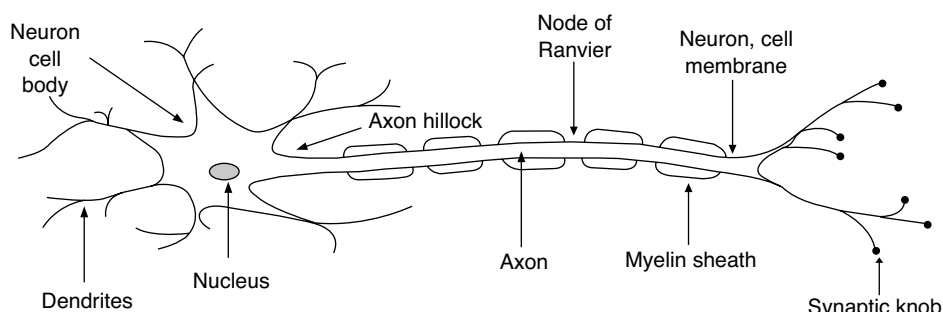

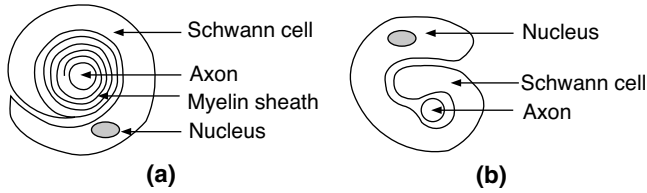**Figure 22.7** ● Schematic diagram of a neuron. Representation of the various branching found in dendrites.

Figure 22.8 ● Representations of myelinated **(A)** and unmyelinated **(B)** axons.

Figure 22.9 ● Representation of the transmission of a nerve impulse along a neuron fiber by saltatory conduction.

varies in length from a few millimeters to a meter or longer. Most axons are too long to transmit the signal to the terminal ending by simple chemical diffusion. Thus, the message received by the neuron cell body is transmitted as an electrical impulse to the axon terminal. The electrical impulse is most often generated at the axon hillock, the region of the cell body where the axon emerges. The electrical impulse is conducted by changes in the electrical potential across the neural membrane. The rate at which the message is transmitted down the axon depends on the thickness of the axon and the presence or absence of myelin. The axon may be bare or it may be surrounded by the membrane of a glial cell that forms a myelin sheath (Fig. 22.8). Between the myelin sheaths are areas of the axonal membrane that are unmyelinated, these bare areas are called the nodes of Ranvier. The nodes of Ranvier allow the nerve impulse to skip from node to node down the length of the axon to increase the speed of the action potential conduction (Fig. 22.9). In unmyelinated neurons, the change in the electrical potential of one part of the membrane causes a change in electrical potential of the adjacent membrane, thus the impulse moves along the axon slower. Nerve impulses travel at speeds of up to 120 m/s in myelinated axons and 10 m/s in unmyelinated axons.

The electrical potential difference between the inner and outer surfaces of the cell membrane is a result of the movement of ions across the membrane. At rest, most neurons have a resting potential of about −70 mV. This means that the inside of the neuron contains more anionic charges than the external side. The ions that move across the nerve membrane and contribute to most of the electrochemical potential are Ca^{2+}, Na^+, K^+, and Cl^-. For a nerve cell to transmit an impulse, the internal charge must increase about 20 mV to −50 mV, the firing threshold for a nerve cell. If this initial depolarization reaches the firing threshold, an action potential will be generated. During an action potential the internal charge will quickly increase to about +35 mV and the membrane is now *depolarized*. This spike is quickly followed by the *hyperpolarization* of the membrane, to
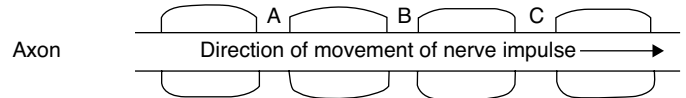
below −70 mV, followed by the return of the membrane to the resting potential (Fig. 22.10). The generation of the action potential from the axon hillock to the terminal end of the nerve may result in the release of neurotransmitters that cross the synaptic cleft to deliver the "message" to the adjacent neuron or target organ.

Neuronal Membrane Ion Permeability During an Action Potential

By definition, the membrane potential is the difference in the polarity of the inside of the cell compared to the outside of the cell, with the outside of the cell conventionally set at 0 mV. During an action potential, the membrane potential changes from a −70 to a +35 mV. Exactly how does a membrane change its electrical potential? It changes its potential by the movement of ions. For an ion to move from one side of the lipophilic membrane to the other, it must go through a channel. There are many specialized protein channels that can change their three-dimensional configuration to allow ions to flow through. If the ion is moving with its concentration gradient, it can simply diffuse through an open channel, no energy would be required. For an ion to move against the electrical gradient, energy is required and the channels are therefore coupled to ATP pumps.

The axolemma is more permeable to K^+ ions than to Na^+ ions. These ions diffuse out of the neuron through the so-called *potassium leak channels*, whose opening does not appear to require a specific membrane change. The movement of K^+ ions is concentration driven; K^+ ions move from inside the neuron, where the concentration is high, to the extracellular fluid, where the concentration is lower. This tendency of K^+ ions to leak out of the neuron (*driven by the concentration gradient*) is balanced to some extent by a limited movement of K^+ ions back into the neuron, both by diffusion through K^+ channels and by active transport mechanisms such as the sodium/potassium ATPase pump. These movements of K^+ result in a potential difference across the membrane, which is a major contributor to the *equilibrium potential* that exists between the opposite faces
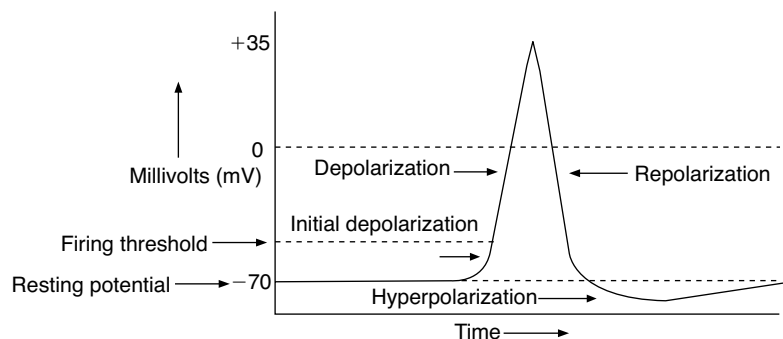

Figure 22.10 ● Changes in electrical potential observed during a nerve impulse.

of a biological membrane in a normal cell at rest with a switched-on sodium pump.

The initial depolarization of the neuron (Fig. 22.10) was shown by Hodgkin and Huxley in 1953 to be a result of increased movement of Na^+ into the neuron, which is followed almost immediately by increased movement of K^+ ions out of the neuron. It is thought that the action potential is triggered by a stimulation that causes a momentary shift of the membrane potential of a small section of the membrane to a less negative value (*depolarization of the membrane*). This causes the gated Na^+ channels in this section of the membrane to open, which allows Na^+ to enter the cell. This process depolarizes the membrane still further, until the action potential reaches a critical value (the *firing threshold*), when it triggers the opening of large numbers of adjacent Na^+ channels so that Na^+ ions flood into the axon. This process continues until the membrane potential of this section of membrane reaches the equilibrium potential for Na^+ ions when the cell is at rest. At this point, all the Na^+ channels of the membrane should be permanently open. This situation is not reached, however, because each channel has an automatic closing mechanism that operates even though the cell membrane is still depolarized. Once closed, the ion channel cannot open again until the membrane potential in its vicinity returns to its original negative value, which is brought about by the leakage of K^+ ions out of the neuron through K^+ channels. Hodgkin and Huxley showed that a membrane becomes more permeable to K^+ ions, a fraction of a millisecond after the Na^+ channels have started to open. As a result, K^+ ions flow out of the neuron, which reduces the electrical potential of the membrane, and so at the peak of the action potential, the membrane potential has a value of about $+40$ mV. The movement of the K^+ ions out of the axon, coupled with the automatic closing of the sodium channel gates and the slower action of the sodium/potassium ATPase pump that transports 3 Na^+ ions out of the neuron for every 2 K^+ ions into the neuron, results in a net flow of positive ions out of the neuron. This briefly *hyperpolarizes* the membrane and causes the membrane potential to drop below its resting potential. As the sodium channels close and K^+ ions flow back into the axon, the membrane potential returns to its resting value. The entire process of depolarization and repolarization is normally accomplished within 1 millisecond.

Ligand-Gated Sodium Channel Structure and Function

Based on mutation studies and electrophysiology studies, a three-dimensional picture relating the structure of the sodium channel to its function is emerging. The sodium channel is a complicated protein with multiple polypeptide sections that are responsible for specific functions of the channel. The channel must (a) be selective for sodium ions, (b) be able to detect and then open when the membrane is slightly depolarized, (c) be able to detect and then close when the membrane becomes hyperpolarized, and (d) convert to a resting state ready to depolarize again. There is much work currently being conducted on all of these functions of the sodium channel.

The mammalian brain sodium channel is comprised of an α subunit and one or more auxiliary β subunits (Figs. 22.11–22.12). The α subunit is composed of four domains (DI–DIV) that fold to make the pore that the sodium ions pass through. Each of the four domains is composed of six transmembrane α-helical segments (S1–S6). The β subunits are involved in the kinetics and voltage dependence of sodium channel opening and closing. The β subunits have large extracellular domains with many sites of glycosylation and only one transmembrane segment.[57]

The sodium channel contains specific amino acids that act as a *selectivity filter*, only allowing sodium ions to pass through the channel. The amino acids that make up the selectivity filter of an ion channel are referred to as the P region. Sodium channels have a P region that gives specificity to sodium ions, whereas potassium and calcium channels have their own P regions that confer selectivity for their respective ions. The selectivity filter of the sodium channel is composed of two rings made up of amino acids from the four homologous domains (DI–DIV). The first ring is composed entirely of negatively charged amino acids. Approximately two to three amino acids deeper into the pore, the second ring is found. The second ring of the P region of the sodium channel is composed of the amino acid sequence DEKA (Asp Glu Lys Ala), whereas the P region of a calcium channel is EEEE (Glu Glu Glu Glu).[58] By selectively mutating the four amino acids from DEKA to EEEE, selectivity for calcium could be conferred to the sodium channels.[59] Other studies also showed that when external solutions where made highly acidic the negative charges of the selectivity filter amino acids could be neutralized ($COO^- \rightarrow COOH$) and ion conductivity decreased.[58]

The sodium channel must also be able to change conformations in response to small changes in the membrane potential. How do sodium channels detect voltage changes and then change shape in response to them? The voltage sensing units of the sodium channels are the S4 segments of the α subunit. These segments contain positively charged amino acids at every third residue. It is postulated that the S4 segments move in response to the change in the local membrane potential and cause a further conformational change that opens the gate of the sodium channel, thus allowing sodium to flow in.[60] The S4 voltage sensors are also responsible for causing conformational changes in the receptor that close the channel to sodium conductance. Exactly how the conformational changes occur is being studied (Fig. 22.12).

Further down the pore of the sodium channel, beyond the selectivity filter lays the putative *local anesthetic binding site* (Fig. 22.13). Site directed mutagenesis studies and molecular modeling studies suggest that local anesthetic binding involves multiple interactions. The positively charged nitrogen of the local anesthetic molecule may form a cation $-\pi$ electron interaction with a phenylalanine residue from the DIVS6 domain.[61,62] The aromatic ring of the anesthetic may also interact with a tyrosine amino acid in the DIVS6 domain. The putative local anesthetic binding site is believed to involve the S6 subunits of the α DI, DIII, and DIV domains. The exact amino acids involved depend on the source and the state of the sodium channel being studied. These studies also suggest that the positively charged nitrogen of the local anesthetic may lie in the center of the pore to create an electrostatic repulsive force that, in addition to the steric block, would prevent sodium ion passage through the pore (Fig. 22.13).[57]
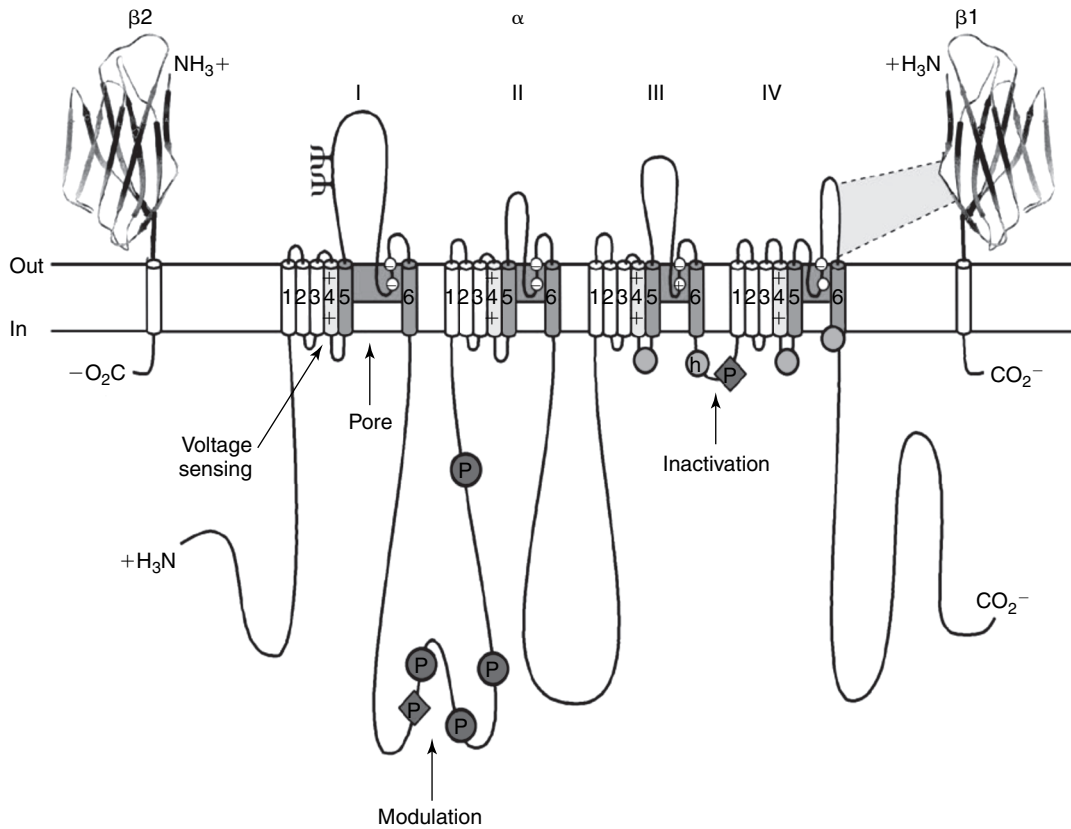
Figure 22.11 ● Structure of voltage-gated sodium channels. Schematic representation of the sodium-channel subunits. The α subunit of the Na$_v$1.2 channel is illustrated together with the β1 and β2 subunits; the extracellular domains of the β subunits are shown as immunoglobulin-like folds, which interact with the loops in the α subunits as shown. Roman numerals indicate the domains of the α subunit; segments 5 and 6 (*dark gray*) are the pore-lining segments and the S4 helices (*light gray*) make up the voltage sensors. Light gray circles in the intracellular loops of domains III and IV indicate the inactivation gate IFM motif and its receptor (h, inactivation gate); P, phosphorylation sites, in dark gray circles, sites for protein kinase A; in dark gray diamonds, sites for protein kinase C; ψ, probable *N*-linked glycosylation site. The circles in the re-entrant loops in each domain represent the amino acids that form the ion selectivity filter (the outer rings have the sequence EEDD and inner rings DEKA). (Reprinted from Catterall, W. A.: Ionic currents to molecular mechanisms: the structure and function of voltage-gated sodium channels. Neuron 26:13–25, 2000, with permission from Elsevier.)
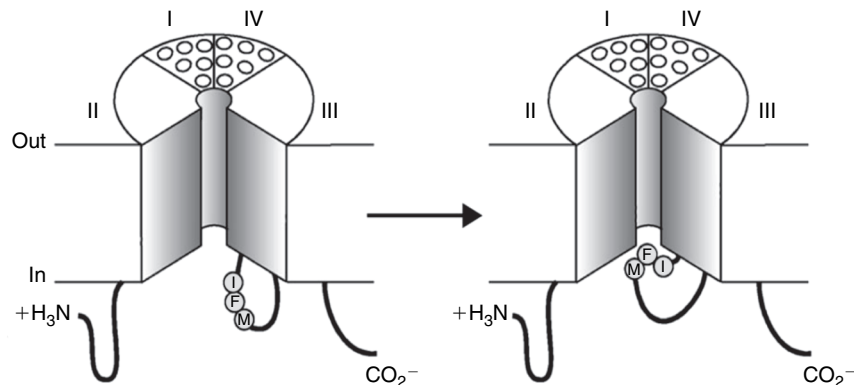

Figure 22.12 ● Mechanism of inactivation of sodium channels. The hinged-lid mechanism. The intracellular loop connecting domains III and IV of the sodium channel is depicted as forming a hinged lid with the critical phenylalanine (F1489) within the IFM motif shown occluding the mouth of the pore during the inactivation process. The circles represent the transmembrane helices. (Reprinted from Catterall, W. A.: Ionic currents to molecular mechanisms: the structure and function of voltage-gated sodium channels. Neuron, 26:13–25, 2000, with permission from Elsevier.)
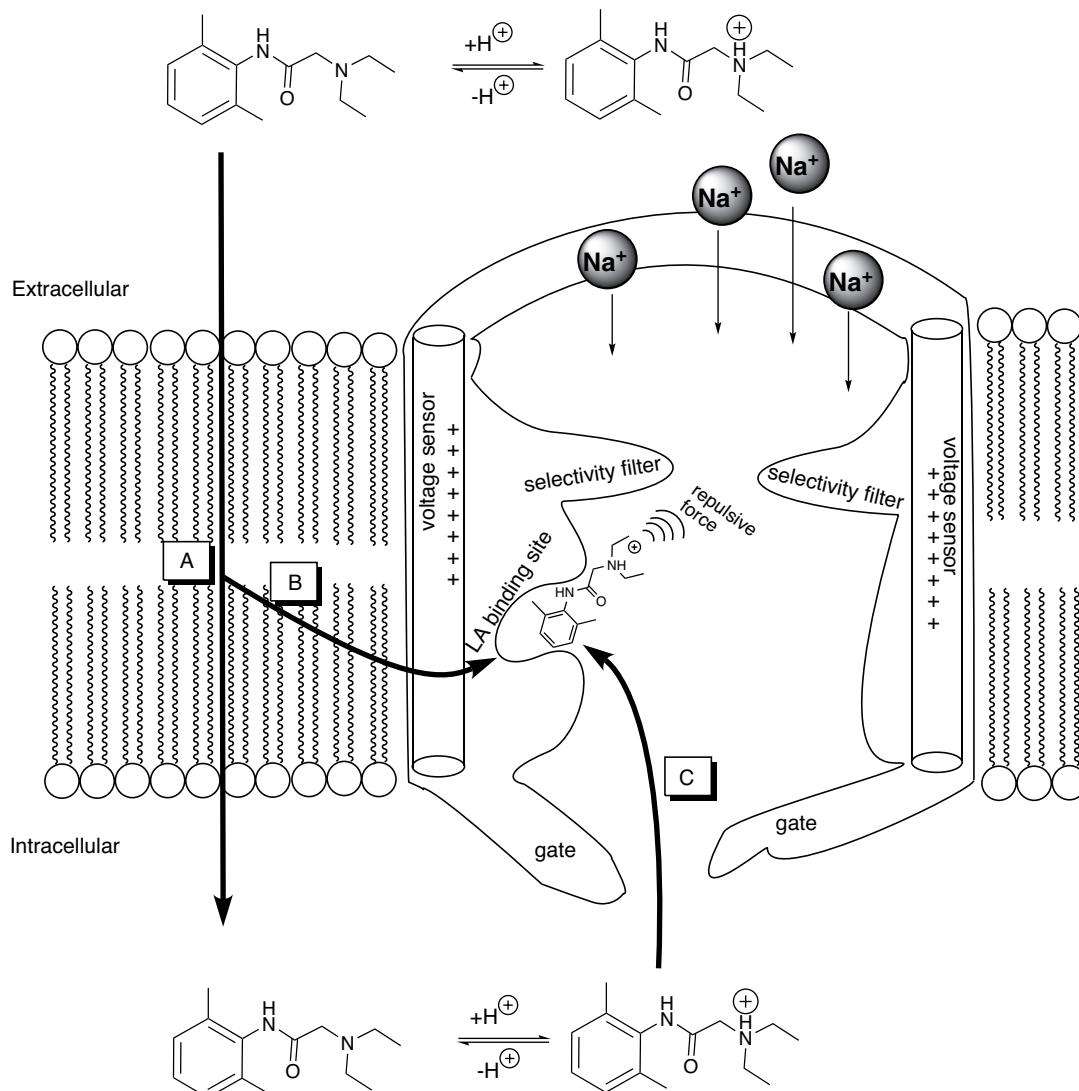
Figure 22.13 ● Proposed mechanism of action of the local anesthetics: **(A)** Hydrophobic pathway into the nerve cell, **(B)** Hydrophobic pathway to the binding site, **(C)** Hydrophilic pathway from the inside of the nerve cell to the binding site. (Adapted with permission from Hille, B.: Local anesthetics: hydrophilic and hydrophobic pathways for the drug-receptor reaction. J. Gen. Physiol. 69:497–515, 1977 and Strichartz, G., et al.: Fundamental properties of local anesthetics. II. Measured octanol: buffer partition coefficients and pKa values of clinically used drugs. Anesth. Analg. 71:158–170, 1990.)

Mechanism of Action of Local Anesthetics

The mechanism of action of the local anesthetics is believed to be via their sodium channel blocking effects. The local anesthetic drug binds to the channel in an area just beyond the selectivity filter or P region (Fig. 22.13). When the local anesthetic binds, it blocks sodium ion passage into the cell and thus blocks the formation and propagation of the action potential. This blocks the transmittance of the message of "pain" or even "touch" from getting to the brain. The ability of a local anesthetic to block action potentials depends on the ability of the drug to penetrate the tissue surrounding the targeted nerve as well as the ability of the drug to access the binding site on the sodium channel.

Local anesthetics do not access the binding site by entering into the sodium channel from the exterior of the neuron. The molecules are too big to pass by the selectivity filter. When local anesthetics are synthesized with a permanent charge, such as compound QX-314 below, they are unable to access the binding site unless they are applied directly to the interior of the neuron.[63] (For more information on QX-314 see "Future Directions," at the end of this chapter.)
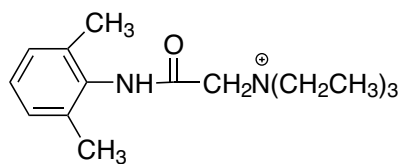
QX-314

If local anesthetics do not access the binding site via the external side, how do they get to their site of action? There is much experimental evidence to show that local anesthetics must access the binding site via a hydrophobic or via a hydrophilic pathway (Fig. 22.13).[64,65] The anesthetics pass through the membrane in their uncharged form (Fig. 22.13 hydrophobic pathway A). In the axoplasm, they reequilibrate with their cationic species. It is postulated that the anesthetic molecule may access the binding site via a hydrophilic pathway by entering into the sodium channel from the interior of the pore, when the channel is open (Fig. 22.13 hydrophilic pathway C). The local anesthetic molecule is believed to bind to the binding site in its ionized form. Another possibility is that before passing all the way through the lipid membrane, the anesthetic may be able to directly access the local anesthetic binding site (Fig. 22.13 hydrophobic pathway B).

Studies using local anesthetics containing a tertiary nitrogen also confirm that the local anesthetic is accessing the binding site from either the hydrophobic or hydrophilic pathways described previously. When this type of anesthetic is applied externally, and the pH of the external media is increased, and thus the local anesthetic is predominantly in the unionized form, the onset of block is more rapid. The neutral form of the drug molecule penetrates the membrane and then accesses the binding site through pathway B or C described in Figure 22.13. The pH of the solution had no effect on sodium conduction block when the local anesthetic used was the neutral molecule benzocaine, suggesting that the change in pH affects the drug charge and not the receptor.[63,66]

The sodium channel has been shown to have a great deal of flexibility and can change shape when the electrical environment around the channel changes. There are at least three conformations that the sodium channel can form. (a) An open state, such as that depicted in Figure 22.12 (drawing on the left) where the sodium ion has a clear pathway from the external side of the membrane to the internal side of the membrane. (b) A "closed/inactive" state shown in Figure 22.12 (drawing on the right), where the sodium channel undergoes a conformational change to prevent sodium ion passage into the cell. The sodium channel undergoes this conformational change in response to the huge influx of sodium causing depolarization of the cell membrane. The sodium channel is now closed and inactive, it cannot open again until the membrane has reached its resting potential. (c) The third conformation of the sodium channel is formed when the membrane potential returns to the resting potential. The sodium channel is now closed but able to open when a stimulus reaches the threshold potential. At this point, the sodium channel is in a "closed/resting" state that is different from the "closed/inactive" state.

The affinity of the local anesthetics for the binding site has complex voltage and frequency dependant relationships. Affinity depends on what state the sodium channel is in as well as the specific drug being tested. In general, at resting states, when the membrane is hyperpolarized, the local anesthetics bind with low affinity. When the membrane has been depolarized and the channel is open, local anesthetics bind with high affinity. Local anesthetics also bind with high affinities when the sodium channel is in the "closed/inactive" conformation, perhaps stabilizing the inactive form of the receptor.

The ability of the local anesthetic to block conduction also depends on the targeted neuron. In general, autonomic fibers, small unmyelinated C fibers (mediating pain sensations), and small myelinated Aγ fibers (mediating pain and temperature sensations) are blocked before the larger myelinated Aγ, Aβ, and Aα fibers (mediating postural, touch, pressure, and motor information).[67]

SARs of Local Anesthetics

The structure of most local anesthetic agents consists of three parts as shown above. They contain (a) a lipophilic ring that may be substituted, (b) a linker of various lengths that usually contains either an ester or an amide, and (c) an amine group that is usually a tertiary amine with a pK_a between 7.5 and 9.0.

1. *The Aromatic Ring*
   The aromatic ring adds lipophilicity to the anesthetic and helps the molecule penetrate through biological membranes. It is also thought to have direct contact with the local anesthetic binding site on the sodium channel. The exact amino acids involved in binding depend on the sodium channel being studied as well as the state (open, closed/inactive, closed/active) of the sodium channel. The aromatic ring is believed to interact with the local anesthetic binding site in a π–π interaction or a π-cation interaction with the S6 domain of the α component of the sodium channel. Substituents on the aromatic ring may increase the lipophilic nature of the aromatic ring. An SAR study of para substituted ester type local anesthetics showed that lipophilic substituents and electron-donating substituents in the para position increased anesthetic activity.[68] The lipophilic substituents are thought to both increase the ability of the molecule to penetrate the nerve membrane and increase their affinity at the receptor site. Buchi and Perlia suggested that the electron-donating groups on the aromatic ring created a resonance effect between the carbonyl group and the ring, resulting in the shift of electrons from the ring to the carbonyl oxygen. As the electronic cloud around the oxygen increased, so did the affinity of the molecule with the receptor (Fig. 22.14).[69] When the aromatic ring was substituted with an electron-withdrawing group, the electron cloud around the carbonyl oxygen decreased and the anesthetic activity decreased as well.

2. *The Linker*
   The linker is usually an ester or an amide group along with a hydrophobic chain of various lengths. In general, when the number of carbon atoms in the linker is increased, the lipid solubility, protein binding, duration of action, and toxicity increases.[70] Esters and amides are bioisosteres having similar sizes, shapes, and electronic structures. The similarity in their structures means that esters and amides have similar binding properties and usually differ only in their stability in vivo and in vitro. For molecules that only differ at the linker functional groups, amides are more stable than esters and thus have longer half-lives than esters. Plasma protein binding may
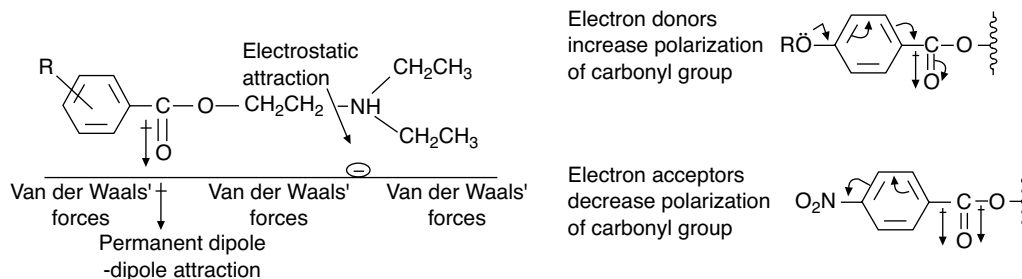
Figure 22.14 • Schematic representation of the binding of an ester-type local anesthetic agent to a receptor site. (Reprinted with permission from Buchi, J., Perlia, X.: Design of local anesthetics. In Ariens, E. J. [ed.] Drug Design. New York, Academic Press, 1972, Vol. 3, p. 243.)

be more prevalent for the amide anesthetics as well, contributing to the increased half-life.[71] Individual drugs are discussed in the drug monograph section.

As described previously, the nature of the substituents on the aromatic ring can affect the electronic nature of the linker and can contribute to the drug's potency and stability. Substituents on the aromatic ring may also confer a steric block to protect the linker from metabolism. Thus, the binding affinity and stability of the anesthetic molecule is affected by the linker as well as the functional groups on the aromatic ring. In general, ester groups are more susceptible to hydrolysis than amide functional groups because of the prevalence of esterases in the blood and the liver. The first ester type local anesthetic synthesized was procaine (Novocain) in 1905. Procaine metabolism can be seen in Figure 22.15. The para-aminobenzoic acid (PABA) metabolite, common to the ester class of drugs, is believed to be responsible for the allergic reactions some patients have experienced with local anesthetics.[72]

3. *The Nitrogen*

Most local anesthetics contain a tertiary nitrogen with a pK_a between 7.5 and 9.5. Therefore, at physiological pH, both the cationic and neutral form of the molecule exists. At physiological pH, the ionized to unionized form of the anesthetic can be calculated using the Henderson-Hasselbalch equation:

$$pH = pK_a + \log ([B]/[BH^+])$$

Extensive work using both internally and externally applied compounds, changing the pH of the solution, and using permanently charged anesthetic analogs has led to the present theory of anesthetic SARs. Namely, that the anesthetic compounds bind to the anesthetic receptor site on the sodium channel in the ionized form. From Figure 22.13, it can be seen that the molecule can penetrate the nerve membrane in its neutral form and then reequilibrate with its cationic form on the internal side of the membrane. Permanently charged, quaternary anesthetics applied to the external side of the nerve membrane do not penetrate and cannot access the local anesthetic binding site.

To keep the anesthetic soluble in commercial solutions, most preparations are acidified. In an attempt to decrease pain on injection and to increase the onset of action, some practitioners advocate adding sodium bicarbonate to the commercial preparation. By adding sodium bicarbonate, the solution will become less acidic and more of the drug will be found in the neutral form. The neutral form will thus cross the nerve membrane quicker and have a quicker onset of action. Although this theoretically makes sense, many studies have found no difference in the onset of action between alkalinized and nonadjusted anesthetics. Manufacturers formulate solutions at a pH that gives them adequate shelf life. When the pH is increased, the stability of the preparation decreases and outright precipitation can occur if too much of the water-soluble cationic form is converted to the anesthetic base. If this practice is followed, very careful titration of the added base is required. The solution should be observed for precipitation and the solution must be used immediately.

Vasoconstrictors Used in Combination with Local Anesthetics

Many anesthetic preparations are commercially available combined with the vasoconstrictor epinephrine. Some anesthetics are also combined with other agents such as norepinephrine, phenylephrine, oxymetolazone, or clonidine to achieve a desired formulation. The epinephrine in the anesthetic solution has multiple purposes. As a vasoconstrictor, the injected epinephrine will constrict capillaries at the injection site and thus limit blood flow to the area. The local anesthetic will thus stay in the immediate area of injection longer and not be carried away to the general circulation. This will help keep the drug where it is needed and allow minimal drug to be absorbed systemically. Thus, anesthetics with epinephrine used for infiltration anesthesia consistently result in lower plasma levels of the anesthetic. This will reduce the systemic toxicity from the anesthetic and increase
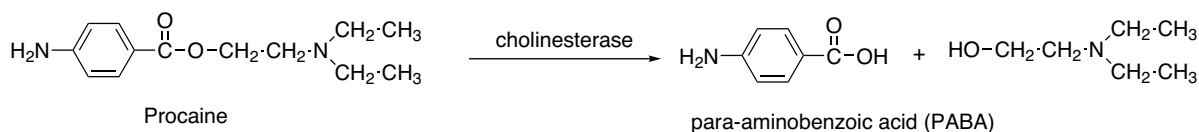

Figure 22.15 • Metabolism of procaine.

the duration of anesthetic activity at the site of injection. The lack of blood flow in the immediate area will also decrease the presence of metabolizing enzymes and this also increase the duration of action of the anesthetic locally. The characteristic blanching that follows epinephrine infiltration anesthesia also makes suturing or manipulating the area easier because of the lack of blood flow in the area. It is not recommended that anesthetics with a vasoconstrictor be used in tissue served by end-arterial blood supply (fingers, toes, earlobes, etc.). This is to prevent ischemic injury or necrosis of the tissue. Epinephrine has also been shown to counteract the myocardial depressant effects of bupivacaine when added to a bupivacaine epidural solution.[73]

Allergic Reactions to Local Anesthetics

True allergic reactions to local anesthetics are very rare. Patients may be allergic to the anesthetic, a metabolite of the anesthetic or a preservative in the anesthetic. Allergies to the ester anesthetics are more common than allergies to the amide anesthetics. As discussed, the ester anesthetics may be metabolized to PABA, which is believed to be responsible for the allergic reactions (Fig. 22.15).

Although the amide type local anesthetics are not metabolized to PABA they may contain a paraben preservative that can be metabolized to PABA like compounds. Parabens are methyl, ethyl, propyl, and butyl aliphatic esters of PABA. In addition to parabens, anesthetics may be preserved with metabisulfites that are also known to cause allergic reactions in sensitive patients, especially patients with asthma.[74] Thus, patients that are allergic to ester type local anesthetics should receive a preservative free amide type anesthetic.

PABA also blocks the mechanism of action of the sulfonamide antibiotics. Sulfonamide antibiotics bind to and inhibit the action of the dihydropteroate synthetase enzyme, the enzyme bacteria used to convert PABA to folate. The inhibition of this enzyme is competitive, therefore if enough PABA is present it will compete with the antibiotic for the binding site on the enzyme and bacterial folate would be synthesized. Thus, there is at least a theoretical reason not to use a PABA forming anesthetic in a patient being treated with a sulfonamide antibiotic.

Methemoglobinemia

Cyanosis as a result of the formation of methemoglobinemia may occur after the administration of the local anesthetics lidocaine,[75] prilocaine,[76,77] and benzocaine.[78] When normal hemoglobin is oxidized by a drug or drug metabolite, it forms methemoglobin. Methemoglobin contains the oxidized form of iron, ferric iron (Fe^{3+}) rather than the reduced ferrous iron (Fe^{2+}) that hemoglobin contains. The oxidized iron cannot bind to oxygen, and methemoglobinemia results when the methemoglobin concentration in the blood reaches 10 to 20 g/L (6%–12% of the normal hemoglobin concentration). Cyanosis results and does not respond to treatment with 100% oxygen. Patients with increased risk factors for developing drug-induced methemoglobinemia include children younger than 2 years, anemic patients, those with a genetic deficiency of glucose-6-phosphate dehydrogenase or nicotinamide adenine dinucleotide methemoglobin reductase or those exposed to excessive doses of the causative local anesthetic. If clinical symptoms of methemoglobinemia occur, treatment is an intravenous infusion of a 1% methylene blue solution, 1 mg/kg body weight, over 5 minutes.

LOCAL ANESTHETIC MONOGRAPHS, INDIVIDUAL PRODUCTS INCLUDING ADVERSE REACTIONS

### The Ester Local Anesthetics

COCAINE
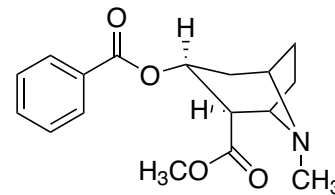
Cocaine

Cocaine was the first agent used for topical anesthesia. It was isolated from the coca leaves that native peoples of the Andes Mountains chew for multiple effects including local anesthesia and stimulant properties to ward off fatigue. Chemists working with the coca alkaloids noticed that the crystals could numb their tongues. In 1884, a German surgeon demonstrated the successful use of cocaine to anesthetize the cornea during eye surgery. One of the most prominent surgeons at Johns Hopkins University, Dr. William Halsted, read about this account and began investigations with cocaine for general surgery. They successfully used cocaine during surgery, but unfortunately Dr. Halsted and several colleagues became addicted.[79] Today, cocaine is used for topical anesthesia of mucous membranes using a 4% to 10% solution. If the solution remains on the membrane for 5 minutes, anesthesia and vasoconstriction of the area will occur. Cocaine has inherent vasoconstrictor properties thus requires no additional epinephrine. The toxicity of cocaine is a result of its vasoconstrictor properties and ability to inhibit catecholamine, including norepinephrine reuptake. Toxic manifestations include excitation, dysphoria, tremor, seizure activity, hypertension, tachycardia, myocardial ischemia, and infarction. Cocaine is used primarily for nasal surgeries, although its abuse potential has resulted in a decrease in use and a search for alternate anesthetics. When cocaine was compared with lidocaine/phenylephrine for nasal intubations, the results were the same with less toxicity in the lidocaine/phenylephrine group.[80]
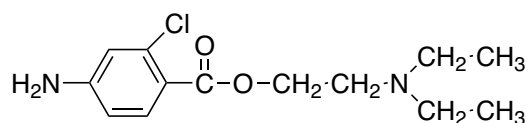
PROCAINE
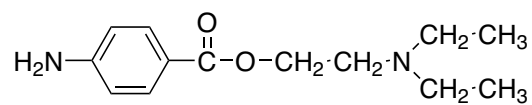
Procaine

Procaine was synthesized in 1904 to address the chemical instability of cocaine and the local irritation it produced. The

pK_a of procaine is 8.9; it has low lipid solubility and the ester group is unstable in basic solutions. Procaine is available in concentrations ranging from 0.25% to 10% with pHs adjusted to 5.5 to 6.0 for chemical stability. Procaine is also included in some formulations of penicillin G to decrease the pain of intramuscular injection. Procaine is very quickly metabolized in the plasma by cholinesterases and in the liver via ester hydrolysis by a pseudocholinesterase (Fig. 22.15). The in vitro elimination half-life is approximately 60 seconds. Any condition that decreases the cholinesterase concentration may increase exposure to procaine and potential toxicity. Decreased enzyme activity can be found with genetic deficiency, liver disease, malignancy, malnutrition, renal failure, burns, third trimester of pregnancy, and following cardiopulmonary bypass surgery. Ester hydrolysis produces PABA, the compound responsible for the allergic reactions common to the ester anesthetics. Procaine is not used topically because of its inability to pass through lipid membranes and finds use as an infiltration agent for cutaneous or mucous membranes, for short procedures. Procaine is also used for peripheral nerve block and as an epidural agent to diagnose pain syndromes.[73]
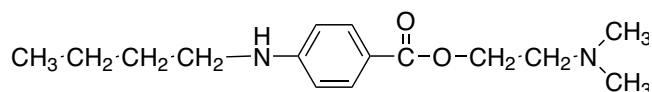
CHLOROPROCAINE

2-Chloroprocaine

The 2 chloride substitution on the aromatic ring of chloroprocaine is an electron-withdrawing functional group. Thus, it pulls the electron density from the carbonyl carbon into the ring. The carbonyl carbon is now a stronger electrophile and more susceptible to ester hydrolysis. Therefore, chloroprocaine has a more rapid metabolism than procaine. The in vitro plasma half-life is approximately 25 seconds. The 2-chloro-4-aminobenzoic acid metabolite precludes this from being used in patients allergic to PABA. The very short duration of action means that this drug can be used in large doses for conduction block (with rapid onset and short duration of action.) As with procaine, a decrease in the plasma cholinesterase activity will prolong the half-life. The pK_a of the chloroprocaine alkyl amine is 9.0 and thus chloroprocaine is almost exclusively ionized at physiological pH. Chloroprocaine is formulated with a pH between 2.5 and 4.0 using hydrochloric acid. The acidic pH of the formulation is responsible for considerable irritation and pain on injection.

Chloroprocaine is used for cutaneous or mucous membrane infiltration for surgical procedures, epidural anesthesia (without preservatives) and for peripheral conduction block.

TETRACAINE

Tetracaine

Tetracaine was developed to address the low potency and short duration of action of procaine and chloroprocaine. The addition of the butyl side chain on the para nitrogen increases the lipid solubility of the drug and enhances the topical potency of tetracaine. The plasma half-life is 120 to 150 seconds. Topically applied tetracaine to unbroken skin requires 30 to 45 minutes to confer topical anesthesia. Tetracaine 4% gel is superior than eutectic mixture with lidocaine (EMLA) (an emulsion of lidocaine and prilocaine) in preventing pain associated with needle procedures in children.[81] Tetracaine metabolism is similar to procaine ester metabolism yielding parabutylaminobenzoic acid and dimethylaminoethanol and conjugates excreted in the urine. The pK_a of the dimethylated nitrogen is 8.4 and tetracaine is formulated as a hydrochloride salt with a pH of 3.5 to 6.0. The increased absorption from topical sites has resulted in reported toxicity. Overdoses of tetracaine may produce central nervous system (CNS) toxicity and seizure activity with fatalities from circulatory depression reported.[82] No selective cardiac toxicity is seen with tetracaine although hypotension has been reported. Tetracaine is employed for infiltration anesthesia, spinal anesthesia, or topical use.

BENZOCAINE
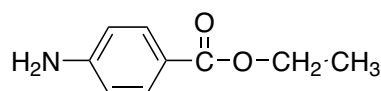
Benzocaine

Benzocaine is a unique local anesthetic because it does not contain a tertiary amine. The pK_a of the aromatic amine is 3.5 ensuring that benzocaine is uncharged at physiological pH. Because it is uncharged, it is not water soluble but is ideal for topical applications. The onset of action is within 30 seconds and the duration of drug action is 10 to 15 minutes. Benzocaine is used for endoscopy, bronchoscopy, and topical anesthesia. Benzocaine is available as a 20% solution topical spray, in a 1% gel for mucous membrane application, and a 14% glycerin suspension for topical use in the outer ear.

Toxicity to benzocaine can occur when the topical dose exceeds 200 to 300 mg resulting in methemoglobinemia. Infants and children are more susceptible to this and methemoglobinemia has been reported after benzocaine lubrication of endotracheal tubes and after topical administration to treat a painful diaper rash.[83,84]

The Amino Amide Local Anesthetics
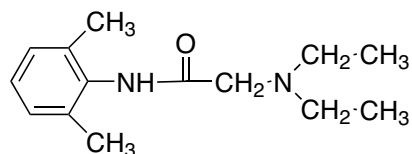
LIDOCAINE

Lidocaine

Lidocaine was the first amino amide synthesized in 1948 and has become the most widely used local anesthetic. The tertiary amine has a pK_a of 7.8 and it is formulated as the hydrochloride salt with a pH between 5.0 and 5.5. When lidocaine is formulated premixed with epinephrine the pH of the solution is adjusted to between 2.0 and 2.5 to prevent
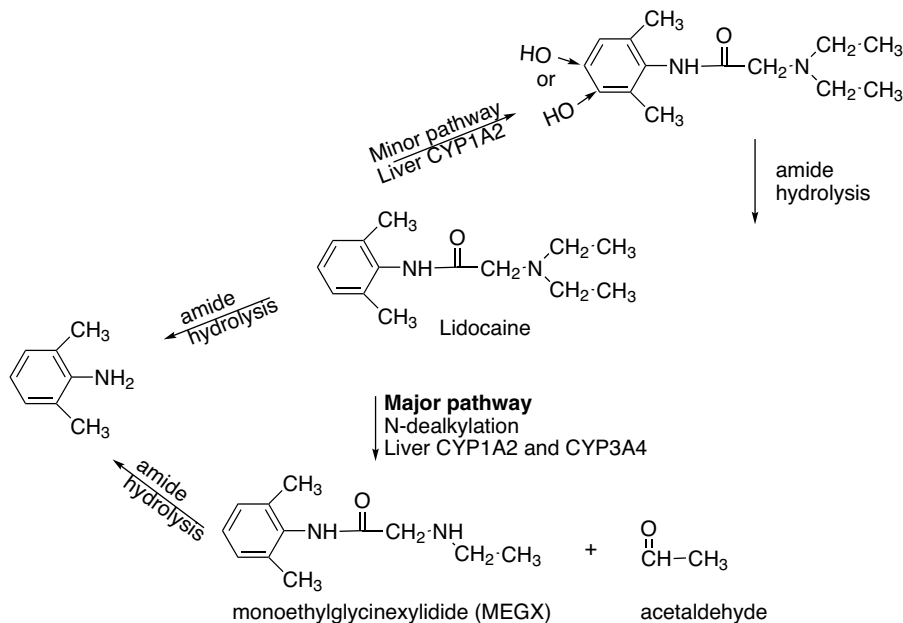
Figure 22.16 ● Metabolism of lidocaine.

the hydrolysis of the epinephrine. Lidocaine is also available with or without preservatives. Some formulations of lidocaine contain a methylparaben preservative that may cause allergic reactions in PABA-sensitive individuals. The low pK$_a$ and medium water solubility provide intermediate duration of topical anesthesia of mucous membranes. Lidocaine can also be used for infiltration, peripheral nerve and plexus blockade, and epidural anesthesia.

The metabolism of lidocaine is typical of the amino amide anesthetics and is shown in Figure 22.16. The liver is responsible for most of the metabolism of lidocaine and any decrease in liver function will decrease metabolism. Lidocaine is primarily metabolized by de-ethylation of the tertiary nitrogen to form monoethylglycinexylidide (MEGX). At low lidocaine concentrations, CYP1A2 is the enzyme responsible for most MEGX formation. At high lidocaine concentrations, both CYP1A2 and CYP3A4 are responsible for the formation of MEGX. The amide functional group is fairly stable because of the steric block provided by the ortho methyl groups although amide hydrolysis products are reported.[85–87]

The toxicity associated with lidocaine local anesthesia is low when used at appropriate doses. Absorption of lidocaine will be decreased with the addition of epinephrine to the local anesthetic. Toxicity increases in patients with liver disease and those with acidosis, which decreases plasma protein binding of lidocaine. CNS toxicity is low with seizure activity reported with high doses. The cardiac toxicity of lidocaine is manifested by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest and death.

MEPIVACAINE
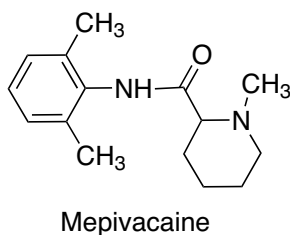
Mepivacaine

Mepivacaine hydrochloride is available in 1% to 3% solutions and is indicated for infiltration anesthesia, dental procedures, peripheral nerve block, or epidural block. The onset of anesthesia is rapid, ranging from about 3 to 20 minutes for sensory block. Mepivacaine is rapidly metabolized in the liver with 50% of the administered dose excreted into the bile as metabolites. The metabolites are reabsorbed in the intestine and excreted in the kidney with only a small percentage found in the feces. Less than 5% to 10% of the administered dose is found unchanged in the urine. The primary metabolic products are the *N*-demethylated metabolite and the 3 and 4 phenolic metabolites excreted as their glucuronide conjugates.

PRILOCAINE
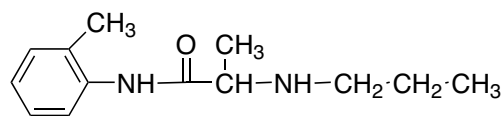
Prilocaine

Prilocaine hydrochloride is a water-soluble salt available as a solution for nerve block or infiltration in dental procedures. Prilocaine is used for intravenous regional anesthesia as the risk of CNS toxicity is low because of the quick metabolism. Prilocaine prepared in the crystal form is used in EMLA for topical administration to decrease painful needle sticks in children. Prilocaine 4% solution should be protected from light and the manufacturer recommends discarding if the solution turns pinkish or slightly darker than light yellow. Solutions are available in various concentrations up to 4%, with or without epinephrine and with or without preservatives.

The pK$_a$ of the secondary amine is 7.9 and commercial preparations have a pH of 5.0 to 5.6. Prilocaine has only one ortho substitution on the aromatic ring, making it more susceptible to amide hydrolysis and giving it a shorter duration
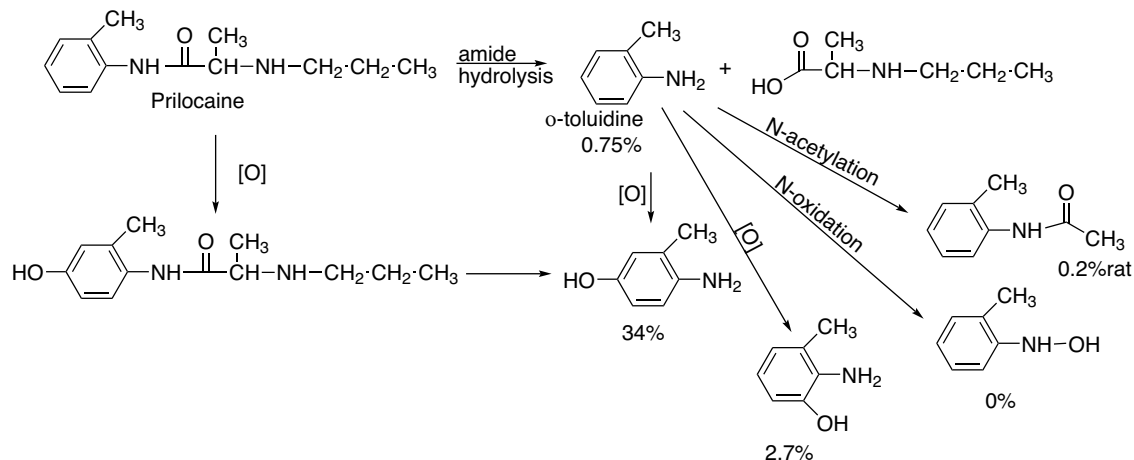
Figure 22.17 ● Metabolism of prilocaine.

of action than lidocaine. Prilocaine metabolism has been studied extensively in animal models, less is known about the human metabolites or the human CYP enzymes involved in their formation (Fig. 22.17).[88,89] The metabolism of prilocaine in the liver yields *o*-toluidine, which is a possible carcinogen. Many aromatic amines, including *o*-toluidine have been shown to be mutagenic, and metabolites of *o*-toluidine have been shown to form DNA adducts. Metabolites of *o*-toluidine are also believed to be responsible for the methemoglobinemia observed with prilocaine use. To decrease the potential for methemoglobinemia, strict adherence to the maximum recommended dose should be followed. Metabolism of prilocaine is extensive with less than 5% of a dose excreted unchanged in the urine.

ETIDOCAINE
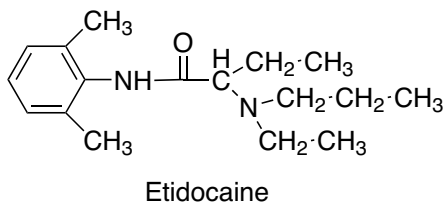
Etidocaine

Etidocaine differs from lidocaine by the addition of an alkyl chain and the extension of one ethyl group on the tertiary amine to a butyl group. The additional lipophilicity gives etidocaine a quicker onset, longer half-life, and an increased potency compared with lidocaine. This may make etidocaine desirable for use when A and C nerve fibers are being anesthetized for long surgical procedures (>2 hours).[90] The tertiary nitrogen pK$_a$ is 7.74, which is similar to lidocaine's pK$_a$ (7.8).

Etidocaine is the most potent amino amide local anesthetic and is used for epidural anesthesia, topical anesthesia, and for peripheral nerve or plexus block. Etidocaine blocks large fast-conducting neurons quicker than the sensory neurons and may leave epidural patients unable to move yet sensitive to painful procedures.[73] Etidocaine has the same potential for cardiac toxicity as bupivacaine and the decreased reports probably are results of the decreased use of etidocaine.

### BUPIVACAINE AND LEVOBUVACAINE
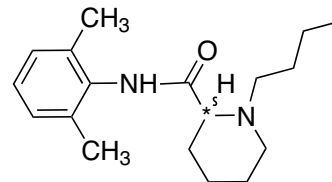
Bupivacaine
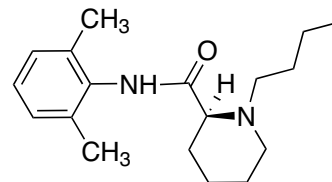
Levobupivacaine S (-)

Bupivacaine was synthesized simultaneously with mepivacaine in 1957 but was at first overlooked because of the increased toxicity compared with mepivacaine. When the methyl on the cyclic amine of mepivacaine is exchanged for a butyl group the lipophilicity, potency and the duration of action all increase. Literature reports of cardiovascular toxicity, including severe hypotension and bradycardia, are abundant in the literature.[91] Bupivacaine is highly bound to plasma proteins (95%), and thus the free concentration may remain low until all of the protein binding sites are occupied. After that point, the plasma levels of bupivacaine rise rapidly and patients may progress to overt cardiac toxicity without ever showing signs of CNS toxicity.[92] The cardiotoxicity of bupivacaine is a result of its affinity to cardiac tissues and its ability to depress electrical conduction and predispose the heart to reentry types of arrhythmias. The cardiotoxicity of bupivacaine was found to be significantly more prominent with the "R" isomer, or the racemic mixture, thus the "S" stereoisomer is now on the market as levobupivacaine.[93]

Levobupivacaine is the pure "S" enantiomer of bupivacaine and in vivo and in vitro studies confirm that it does not undergo metabolic inversion to R(+) bupivacaine. The pK$_a$ of the tertiary nitrogen is 8.09, the same as bupivacaine's

pK_a. Levobupivacaine is available in solution for epidural administration, peripheral nerve block administration, and infiltration anesthesia. Clinical trials have shown that levobupivacaine and bupivacaine have similar anesthetic effects.[94] Levobupivacaine has lower CNS and cardiotoxicity than bupivacaine although unintended intravenous injection when performing nerve blocks may result in toxicity. Racemic bupivacaine is metabolized extensively with no unchanged drug found in the urine or feces. Liver enzymes including the CYP3A4 and CYP1A2 isoforms are responsible for *N*-dealkylation and 3-hydroxylation of levobupivacaine followed by glucuronidation or sulfation.[95]

ROPIVACAINE
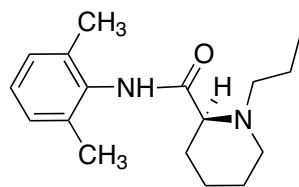
Ropivacaine

The recognized increase in cardiotoxicity of one bupivacaine isomer led to the stereospecific production of ropivacaine as the single "S" (−) enantiomer. Ropivacaine is the propyl analog of mepivacaine (methyl) and bupivacaine (butyl). The pK_a of the tertiary nitrogen is 8.1, and it displays the same degree of protein binding as bupivacaine (~94%). Although ropivacaine has similar properties as bupivacaine, it displays less cardiotoxicity. The shortened alkyl chain gives it approximately one third of the lipid solubility of bupivacaine. Animal studies have shown that ropivacaine dissociates from cardiac sodium channels more rapidly than bupivacaine. This decreases the sodium channel block in the heart and may be responsible for the reduced cardiotoxicity of ropivacaine.[92]

Ropivacaine undergoes extensive metabolism in humans with only 1% of a dose excreted unchanged in the urine.[96] Four metabolites of ropivacaine have been identified from human liver microsome incubations and in vivo studies. The CYP1A2 isoform was found to be responsible for the formation of 3-OH ropivacaine, the primary ropivacaine metabolite. The CYP3A4 isoform was responsible for the formation of 4-OH ropivacaine, 2-OH methyl-ropivacaine, and the *N*-dealkylated metabolite (S)-2′,6′-pipecoloxylidide.[97] Coadministered inhibitors of CYP1A2 may be of clinical importance, CYP3A4 inhibitors seem to be of less clinical relevance.[98]

Ropivacaine is a long-acting amide-type local anesthetic with inherent vasoconstrictor activities, so it does not require the use of additional vasoconstrictors. It is approved for epidural, nerve block, infiltration, and intrathecal anesthesia.

DIBUCAINE
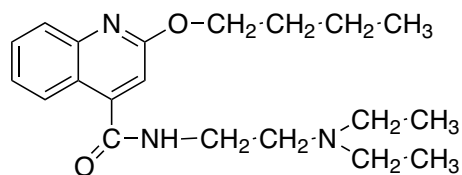
Dibucaine

Dibucaine is a topical amide anesthetic available in over-the-counter creams and ointments used to treat minor conditions such as sunburns and hemorrhoids. Dibucaine has been found to be highly toxic when taken orally, inducing seizures, coma, and death in several children who accidentally ingested it.[99] Metabolites of dibucaine identified in the urine of rats, rabbits, and humans included hydroxylated metabolites of the quinoline ring, monohydroxylated and dihydroxylated metabolites of the *O*-alkyl side chain (2′- and 3′-position), and the *N*-de-ethylated dibucaine metabolite.[100]

ARTICAINE
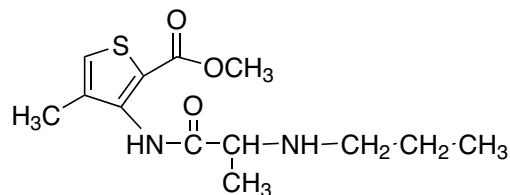
Articaine

Articaine has a secondary nitrogen with a pK_a of 7.8. It contains an aromatic thiophene ring bioisostere of the phenyl ring found in most other amide anesthetics. The log P of a benzene ring is 2.13 and the thiophene ring log P is 1.81, thus the thiophene ring is more hydrophilic than a phenyl ring. Although the thiophene ring has less lipid solubility than a phenyl ring, articaine is a lipid-soluble compound due to the propylamine, the branched methyl and the substitutions on the thiophene ring. The onset of action of articaine is similar to lidocaine's onset of action. Articaine is available in a 4% solution with epinephrine for use in infiltration and nerve block anesthesia.

Articaine is metabolized rapidly via plasma and tissue carboxyesterase to its primary metabolite, the inactive, water-soluble carboxylic acid. Approximately 40% to 70% of articaine administered epidurally is metabolized to the carboxylic acid, articainic acid. Approximately 4% to 15% of the articainic acid undergoes glucuronide conjugation and only 3% of the dose is recovered unchanged in the urine. The rapid plasma metabolism and reported inactivity of the carboxylic acid metabolite make articaine a potentially safer anesthetic agent when multiple or large doses are necessary.[101,102]

Future Directions of Local Anesthetic Research

One of the issues of local anesthetic use is that they are not specific to sensory nociceptors, the "pain neurons." Local anesthetics also block pressure, touch, and motor axons leading to numbness and loss of muscle control. Recent studies in rats have shown that administering the quaternary lidocaine molecule, QX-314, along with capsaicin allows the permanently charged anesthetic access to pain-sensing neurons only. The quaternary charge on QX-314 prevents it from entering all neurons via simple diffusion through the lipophilic membrane. Capsaicin was found to bind to a protein only found on pain-sensing neurons, TRPV1 channels. When capsaicin binds to TRPV1, the channel opens to allow QX-314 to enter the axoplasm and then access the local

anesthetic binding site in the sodium channel from the hydrophilic pathway (Fig. 22.13 hydrophilic pathway C). By specifically blocking the sodium channels of only pain neurons, other nerve function is preserved. This type of pain management would make it possible to have a dental procedure with no pain, yet not leave the entire face numb, or have an epidural during labor and still be able to walk. This is an exciting new opportunity in pain management that is undergoing research presently.[103]

Another area of research is the formulation of local anesthetic liposomes and microspheres. The principle behind this research is that the local anesthetic molecules are amphipathic, with both a hydrophilic and hydrophobic component. The anesthetic molecule can be suspended inside carrier substances made of egg phospholipids and cholesterol liposomes or biodegradable polymers of lactic acid or glycolic acid. The carrier molecule will allow a controlled delivery of the local anesthetic and provide a long duration of action, potentially with less systemic toxicity.[91,104] Carrier molecules are also being designed that combine a local anesthetic with an opioid analgesic that may offer alternative analgesic delivery methods.[105]


◆ R E V I E W   Q U E S T I O N S ◆

1. A nurse anesthetist calls the OR pharmacy to discuss a patient history and get your input on choosing a general anesthetic for an upcoming operation.

   ML is a 32-year-old, 5′4″, 460-pound woman who is scheduled for an elective gastroplasty (stomach stapling). She has a history of hypertension (150/98 mm Hg), hyperlipidemia (LDL-cholesterol = 140mg/dL), and a large stage III pressure ulcer on her lower back. The last time that the patient underwent surgery, she could not be roused from the sedation and spent 24 hours in the postanesthetic care unit (PACU). Her prior surgery required 3 hours of general anesthesia maintained with isoflurane. The nurse anesthetist would like to know if one of the other formulary agents offers a shorter recovery time. General anesthetics on the formulary include nitrous oxide, desflurane, sevoflurane, isoflurane, enflurane, and halothane.

2. A medical student was assigned the task of debriding ML's decubitus ulcer and calls the pharmacy to obtain procaine to inject locally before beginning the painful procedure. You review the patient's chart for allergies (no known drug allergies [NKDA]) and notice that the patient is also receiving 1% silver sulfadiazine cream to prevent bacterial colonization of the ulcer. You recommend against using the procaine and suggest a 1% lidocaine with epinephrine instead. Why?

3. An anesthesiologist from the obstetric unit calls to request stat delivery of 20% intralipid to treat an inadvertent intravascular injection of bupivacaine. The patient is in cardiac arrest. Why is the anesthesiologist requesting intralipid?

4. TG, a 45-year-old male woodworker, presents to the ER with an injured index finger. While cleaning a circular saw blade, he accidentally severed the tip (fleshy part, no bone) of his finger. The ER resident calls to request lidocaine 2% with epinephrine 1:200,000 to decrease the pain associated with suturing. You suggest an alternate. Why did you NOT fill the original requested anesthetic?

5. JF, a patient with a severe allergic reaction to 2-chloroprocaine, is having plastic surgery to remove three moles from her face. The physician calls to request your input in choosing a local anesthetic. The plastic surgeon has the five drugs shown at the bottom of this page available in his clinic. Which drug would you recommend that he use?

6. While working as a pharmacy intern at a retail pharmacy, a woman carrying an infant asks you to ring up three tubes of Maximum Strength Vagisil Creme. In conversation with her, you find out that she has been treating her 2-month-old daughter's painful, excoriated diaper rash with the cream for the last week. She claims to have received the advice on a mothers' chat room on the Internet. You observe that her 2-month-old daughter has bluish lips and very pale translucent skin that also has a bluish tint. You immediately advise her to take her daughter to the emergency room. Why?
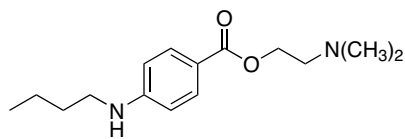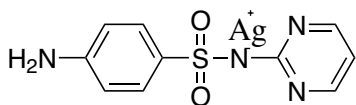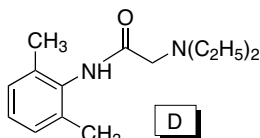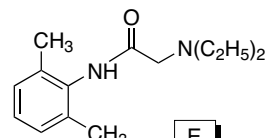

A (Preservative free)
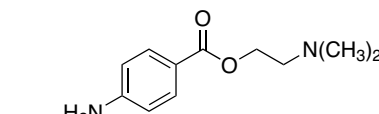
B (Preservative: Methylparaben)
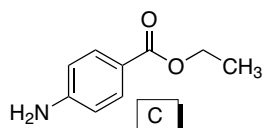
C (Preservative: Benzalkonium chloride)

D (Preservative: Benzalkonium chloride)

E (Preservative: Methylparaben)

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