Chapter 11
Pharmacology of Local Anesthetics

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Contents

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Introduction

The development of local anesthetics dates to the first use by the Incas of Peru, using cocaine for its medicinal properties. They treated headaches with trepanation or by burrowing holes in the skull with chewed cocaine as the local anesthetic [1]. Today, the use of local anesthetics by anesthesia providers has gained increasing popularity, traditionally in both obstetric and regional anesthesia. This chapter will focus on the types of local anesthetics, dosing and mechanism of action, indications with clinical pearls, and drug interactions/toxicity profile.

Drug Classes

The majority of injectable local anesthetics are tertiary amines. Only a few (e.g., prilocaine and hexylcaine) are secondary amines. All local anesthetics are amphipathic and possess both lipophilic and hydrophilic parts. The lipophilic part is the largest portion derived from benzoic acid, aniline, or thiophene. The hydrophilic part is an amino derivative of ethyl alcohol or acetic acid. Local anesthetics that lack a hydrophilic part are mostly used as topical anesthetics (e.g., benzocaine). The structure is completed by an intermediate hydrocarbon chain link which contains either an ester or an amide linkage. Variations in this intermediate chain portion of the basic local anesthetic molecule have resulted in the development of two basic classes of local anesthetics, the esters and the amides.

The ester-type local anesthetics are less stable in solution, are rapidly metabolized by plasma pseudocholinesterase, and appear to be associated with rare true allergic reactions. The amide-type local anesthetics are very stable in solution, are

Table 11.1 Anesthetic agents and their common uses

Agent	Commonly used for	Agent	Commonly used for
Cocaine	Topical	Mepivacaine	Infiltration, PNB, spinal (not FDA approved), epidural
Benzocaine	Topical	Prilocaine	Infiltration, PNB, epidural
Procaine	Infiltration	Bupivacaine	PNB, epidural, spinal, infiltration
Dibucaine	Spinal	Ropivacaine	Infiltration, PNB, epidural
Tetracaine	Spinal	Lidocaine	PNB, spinal, epidural, topical, infiltration
Chloroprocaine	PNB, epidural, infiltration		

PNB peripheral nerve block
Covino B, Vassallo H. Local anesthetics: mechanisms of action and clinical use. Orlando: Grune & Stratton; 1976.

metabolized in the liver by cytochrome P450 enzymes, and are almost never associated with true allergic reactions.

Commonly used amino amides include lidocaine, mepivacaine, prilocaine, bupivacaine, etidocaine, and ropivacaine (Table 11.1). Commonly used amino esters include cocaine, procaine, tetracaine, chloroprocaine, and benzocaine. An easy way to remember which drug belongs in which category is that all of the amino amides contain the letter "i" twice, as does the term "amino amides."

Local Anesthetic Properties

Activity of local anesthetics may be affected by their lipid solubility, percent ionization at physiologic pH, affinity for protein binding, and vasodilatation effect.

Lipid Solubility

Lipid solubility appears to be the most significant property of local anesthetic molecules in determining anesthetic potency. Local anesthetic molecules which are highly lipophilic easily penetrate nerve cell membranes and become intracellular, resulting in more blockades. For example, bupivacaine is considerably more lipid soluble and more potent than lidocaine.

Ionization

Local anesthetics exist in ionized and nonionized forms, the proportions changed by pH of the environment. The nonionized portion is the form that is capable of diffusing across nerve membranes and blocking sodium channels. The nonionized form also

has a faster onset of action due to fast diffusion. Local anesthetics differ in respect to the pH at which the ionized and nonionized forms are present at equilibrium (7.6–8.9). The more closely the equilibrium pH for a given anesthetic approximates the physiologic pH of tissues (i.e., 7.35–7.45), the more rapid the onset of action.

A decrease in pH shifts equilibrium toward the ionized form, delaying onset of action. This explains why local anesthetics are slower in onset of action and less effective in the presence of inflammation, which creates a more acidic environment with lower pH. By addition of sodium bicarbonate to certain local anesthetics, we may enhance the onset of action. Overalkalinization, however, can cause local anesthetic molecules to precipitate from solution [2].

Protein Binding

Protein binding is related to the duration of action. The more firmly the local anesthetic binds to the protein of the sodium channel, the longer the duration of action. Poorly protein-bound agents, such as procaine, are readily washed out in in vitro experiments, and duration of local anesthetic blockade can be extremely short, whereas those which are highly protein bound, such as bupivacaine, are less easily washed out in in vitro experiments, and conduction blockade is interrupted for a longer period of time. The clinical activity of the agents which are more protein bound such as bupivacaine and etidocaine are associated with a longer duration of clinical anesthesia. The less well protein-bound agents such as procaine and chloroprocaine are associated with short duration of clinical activity.

Vasodilatation

Most local anesthetics, with the exception of cocaine, have a biphasic effect on vascular smooth muscle. At low doses, they cause vasoconstriction, and at high doses, they cause vasodilation via direct relaxation of peripheral arteriolar smooth muscle fibers. The more vasodilatory property the local anesthetic has, the faster the absorption and thus the shorter the duration of action of the local anesthetic. To counteract this vasodilatation, epinephrine is often included in local anesthetic solutions [3].

Mechanism of Action

Once the local anesthetic reaches the neuron, it reversibly binds to voltage-gated sodium channels, blocking Na+ movement through the channels and thus blocking the action potential and neural conduction. At adequate dosage, these drugs should reversibly inhibit conduction of all neurons.

Na+ (Sodium) Channels

Na+ channels are heterotrimeric transmembrane proteins, consisting of α (Mr~260 kDa), β1 (36 kDa), and β2 (33 kDa) subunits. The α subunit contains four homologous domains (I–IV); each domain contains 6 α-helical transmembrane segments (S1–S6). The voltage sensor is located in the fourth transmembrane segment of each domain which is rich in positively charged residues. The loop between domains III and IV serves as an inactivation gate which folds to block the pore shortly after opening of the channel. The binding site for local anesthetics is located in the S6 transmembrane domain of segment IV close to the intracellular side of the membrane [4].

Function of Na+ (Sodium) Channels

Na+ (sodium) channels can be found in three states. First, there is the closed state at potentials below –70 mV. The pore in the channel is occluded so that Na^+ ions cannot pass from one side to the other. Second, the open state of the channel is initiated by depolarization of the transmembrane potential to the threshold potential (usually above –40 mV). In response to depolarization, the channel opens within a millisecond and allows Na^+ ions to diffuse down their concentration gradient through the pore, causing an inward current and depolarizing the transmembrane potential even further, which continues a self-driven depolarization [5].

This process underlies the upstroke of the action potential of most excitable cells. During channel opening the S4 segment twists back, driven by both the changed potential difference and intrinsic charge changes, which allow the outer pore mouth to expand, resulting in a 20° twist of the α-helix. The third state follows activation during prolonged depolarization and is termed the inactivated state. The inactivated state was shown to be a nonconducting mode of the channel. The order of affinity of local anesthetics for different sodium channel states is open, inactivated, and lastly, resting. Thus, the open state of the sodium channel is the primary target of local anesthetic molecules. The blocking of propagated action potentials is therefore a function of the frequency of depolarization.

Mechanism of Differential Blockade

After administration of local anesthetics, molecules diffuse from the extraneural site toward the nerves. The rate of diffusion depends on several factors; the most significant of which is the concentration gradient. The greater the initial concentration of the local anesthetic, the faster is the diffusion of its molecules and the more rapid its

Table 11.2 Short- and long-acting anesthetic agents

Short-acting agents	Long-acting agents
Procaine, lidocaine, mepivacaine, prilocaine, chloroprocaine	Tetracaine, bupivacaine, etidocaine, ropivacaine

onset of action. It is important to note that the fasciculi that are located near the surface of the nerve are termed mantle bundles and are reached by the local anesthetic first and blocked completely. The fasciculi found closer to the center of the nerve are called core bundles and are exposed to less concentrated anesthetic solution and delayed response [6].

Thus, small unmyelinated C fibers (pain) and small myelinated Aδ fibers (pain and temperature) are blocked before larger myelinated Aγ, Aβ, and Aα fibers (postural, touch, pressure, and motor signals). In large nerve trunks, motor nerves are usually located circumferentially and may be affected before the sensory fibers. In the extremities, proximal sensory fibers are located more circumferentially than distal sensory fibers. Thus, loss of sense may spread from proximal to distal part of the limb.

It is important to understand that nerves with higher firing frequency and more positive membrane potential are more sensitive to local anesthetic block because the charged (active form) local anesthetic molecules are more likely to access to the binding sites in the open Na+ channel and less likely to dissociate from its binding sites in the open or inactivated channels in comparison with the resting Na+ channels. Sensory fibers, especially pain fibers, have a high firing rate and relatively longer action potential duration than motor fibers and thus are more sensitive to lower concentrations of local anesthetics.

Indications/Clinical Pearls

Local anesthetics are commonly used for the blockade of nerve impulses to abolish a specific sensorimotor function. Specifically, local anesthetics bind to voltage-gated Na+ channels, blocking electrical impulses propagated by neuronal action potentials.

There are many uses of local anesthetics. These include topical applications, injection around nerve endings via peripheral nerve blockade, intrathecal or epidural injections, or intravascular injections for arrhythmia management (see Table 11.2).

In our practice, local anesthetics are most commonly used for peripheral nerve blocks; intravenous regional anesthesia, i.e., Bier blocks; topical and infiltration anesthesia; and neuroaxial blocks. In addition, lidocaine is used as a ventricular antiarrhythmic. In plastic surgeon offices, local anesthesia is also used as tumescent anesthesia. The type and quantity of local anesthetic depends on the type of nerve block, surgical procedure, and physical status of the patient.

Table 11.3 Anesthetic drugs and their suggested max dose

Drug (per 70 kg patient)	Concentration %	Volume CC	Suggested max dose (mg)
Lidocaine	1–2	30–50	500
Mepivacaine	1–1.5	30–50	500
Prilocaine	1–2	30–50	600
Bupivacaine	0.25–0.5	30–50	225
Levobupivacaine	0.25–0.5	30–50	225
Ropivacaine	0.2–0.5	30–50	250

Peripheral Nerve Blocks

A significant difference exists between the onset times of various agents when blocks are done for peripheral nerves. In general, agents of intermediate potency have a more rapid onset than the more potent compounds do. Onset times of approximately 14 min for lidocaine and mepivacaine have been reported versus approximately 23 min for bupivacaine. Epinephrine will increase the duration of most local anesthetics for peripheral nerve blocks, but should not be used for ankle or digit blocks for risk of ischemia (Table 11.3).

When combining two local anesthetics for a given block, usually a short-acting local anesthetic for surgical anesthesia is used, with the combination of a long-acting agent for postoperative pain control. It is recommended to not use the maximum doses for two local anesthetics in combination, because the toxicities are additive [7].

Topical and Infiltrative Local Anesthesia

Infiltrative

All local anesthetics have an immediate onset of action and any local anesthetic may be used for infiltration anesthesia. Duration of action varies and depends on the type of local anesthetic used. Epinephrine can be used to prolong the duration, and it is more pronounced when added to lidocaine. Dilute concentrations will provide equal analgesia.

Topical

Lidocaine, cocaine, dibucaine, tetracaine, and benzocaine are most commonly used for short duration of topical analgesia. EMLA cream, which is a combination of lidocaine and prilocaine, can be used for IV placements. Tetracaine and lidocaine sprays are available for endotracheal intubation, bronchoscopies, and endoscopies.

Intravenous

Bier block is a technique for intravenous regional anesthesia. It traditionally requires 3 mg/kg of low-concentration short-acting agents such as 0.5 % prilocaine or lidocaine without epinephrine. It is not recommended to use bupivacaine for intravenous regional

anesthesia as it is associated with local anesthetic toxicity and death [8]. Dilute solutions of long-acting amide and adjuvants such as tramadol, ketorolac, or clonidine have been used to prolong sensory blockade and analgesia after deflation of the tourniquets [9]. Bier blocks can be used for both upper- and lower-extremity surgeries.

Central Neuroaxial Block

Epidural

Any of the local anesthetic drugs may be used for epidural anesthesia. Potency affects duration of action, with the long-acting agents producing analgesia for 3–4 h and intermediate agents for about 1–2 h. Procaine and tetracaine are rarely used because of their long onset times. Interestingly, the duration of short- and intermediate-acting drugs is significantly prolonged by the addition of epinephrine (1:200,000), but the duration of long-acting drugs is minimally prolonged.

Clinical Pearl

Local anesthetics can be used for differential inhibition of sensory and motor activity. They have a unique property of having a motor-sparing effect; low concentrations will allow for a motor-sparing sensory blockade. Bupivacaine is widely used in obstetrics and for postoperative pain management for its ability of differential inhibition at varying concentrations. Low concentrations will have a motor-sparing effect while providing adequate sensory analgesia.

Increasing the dosage of the local anesthetic can increase the duration of satisfactory anesthesia. This is done by administering either a larger volume or a more concentrated solution. Increasing the concentration of epidurally administered local anesthetic while maintaining the same volume of injectate results in shorter latency, an improved incidence of satisfactory analgesia, and a longer duration of sensory analgesia [10].

Clinical Pearl

Caution should be taken in pregnant patients, as nerve tissue is particularly sensitive to local anesthetics. Lower doses or local anesthetics should be used (Table 11.4).

Spinal

Most of the local anesthetics can be used intrathecally. Caution must be taken with the intermediate local anesthetics such as mepivacaine or lidocaine, as they have an increased incidence of limited transient neurologic symptoms (back pain, paresthesias, radicular pain, or hypoesthesia) [11, 12]. Long-acting agents like bupivacaine are less likely to do so.

Clinical Pearl

The spread of the local anesthetic in the intrathecal space is determined by the baricity of the solution, positioning of the patient immediately after placement, and dose of the injectate.

Table 11.4 Anesthetic drugs and their concentrations for pregnant patients

Drug	Concentration (%)	Volume (cc)
Procaine	10.0	1–2
Lidocaine	1.5, 5.0	1–2
Mepivacaine	4	1–2
Tetracaine	0.25–1.0	1–4
	0.25	2–6
	1.0	1–2
Bupivacaine	0.5	3–4
	0.75	2–3
Levobupivacaine	0.5	3–4
	0.75	2–3
Ropivacaine	0.5	3–4
	0.75	2–3

Tumescent Anesthesia

This is a new technique in the use of local anesthetics for plastic surgery use. During liposuction procedures, surgeons will inject subcutaneously large volumes of dilute local anesthetic in combination with epinephrine. Caution must be taken to prevent adverse outcomes, because very large doses are typically used, typically of lidocaine 35–55 mg/kg [13].

Dosing Options

Absorption of local anesthetics is affected by the following factors: dosage, site of injection, speed of administration, local tissue vascularity, drug-tissue binding, pH, and presence of vasoconstricting drugs.

The maximum dose of each local anesthetic varies as seen in Table 11.2. As seen there is variability in the maximum dosage with and without addition of epinephrine. Since local anesthetics are vasodilators, they tend to be absorbed into the bloodstream from the operative field because of vasodilatation of peripheral arterioles especially in vey vascular tissues. Epinephrine induces vasoconstriction, delaying absorption of the local anesthetic for longer duration of action at the site of injection. By delaying absorption, epinephrine also increases the safe dose of local anesthetic that may be administered.

Each patient situation must be taken into account given that protein binding is an important factor in dosing of local anesthetics. Decreasing protein binding allows more free drugs to be available. For example, in parturient patients, the local anesthetics are more potent and there is a higher level of free drugs, therefore toxicity, in blood due to decreased protein binding.

Bicarbonate is another drug that is commonly added to local anesthetic solutions, particularly when the patient is awake. Because the pH of local anesthetic solutions is generally 4–5 to prolong shelf life, patients often experience burning on injection. Bicarbonate also helps in onset of medication by increasing the nonionic form of the local anesthetic and allowing faster diffusion through tissue. Addition of sodium bicarbonate decreases the latency of onset and increases potency of local anesthetics.

Speed of administration is also important because toxicity develops as a result of peak serum concentration. When multiple areas are to be anesthetized with local anesthetic, inject each site sequentially rather than all at once at the beginning of the procedure. If an area will not be operated on at the beginning of the procedure, wait to inject it until ready to extend the procedure to that site. This spreads the total dose of local anesthetic over a longer period, leading to lower peak serum levels.

Drug Interactions

Ester local anesthetics are rapidly metabolized in the blood via pseudocholinesterases [14]. Amide-type local anesthetics are metabolized by the liver. Anything that reduces hepatic blood flow, i.e., liver or heart failure or certain classes of medications, will increase the likelihood of local anesthetic toxicity. Drugs such as B-blockers and H2 receptor blockers may inhibit cytochrome CYP2D6, responsible for the local anesthetic metabolism [14]. Itraconazole inhibits CYP3A4 and may decrease bupivacaine elimination by 20–25 % [15].

Local Anesthetic Side Effects

Allergic Reactions

These are usually more common with esters, which are infrequently used, since they are derivatives of para-aminobenzoic acid which is a well-recognized allergen. They usually contain methylparaben as a preservative, which is a neurotoxin. Allergy to amides though extremely rare can occur. The reactions range from hypersensitivity to anaphylaxis [16].

Methemoglobinemia

A side effect unique to prilocaine is methemoglobinemia at doses of at least 600 mg. The liver metabolizes prilocaine to o-toluidine which oxidizes hemoglobin to methemoglobin. It is clinically insignificant in healthy adults with normal oxygen-carrying capacity but can cause hypoxemia in infants. Methemoglobinemia is readily treated with methylene blue [17].

Myotoxicity

Skeletal muscle toxicity is a rare and uncommon side effect of local anesthetic drugs. Intramuscular injections of these agents regularly result in reversible myonecrosis. The extent of muscle damage is dose dependent and worsens with serial or continuous administration. All local anesthetic agents that have been examined are myotoxic, whereby procaine produces the least and bupivacaine the most severe muscle injury [18].

Neurotoxicity

In the late 1970s and early 1980s, prolonged sensory and motor deficits were reported in some patients after the epidural or subarachnoid injection of large doses of chloroprocaine. Some studies suggest that the combination of low pH, sodium bisulfite, and inadvertent intrathecal dosing is responsible in part for the neurotoxic reactions observed after the use of large amounts of chloroprocaine solution; other studies have disputed this claim and note that chloroprocaine itself at high concentrations can also be neurotoxic, but these concentrations are probably rarely achieved during properly positioned epidural anesthesia, as opposed to inadvertent spinal anesthesia [19].

Transient Neurologic Syndrome

Single-shot spinal anesthesia with commonly recommended doses and concentrations of many different local anesthetics can produce more limited and transient neurologic symptoms (back pain, paresthesia, radicular pain, or hypoesthesia). The addition of vasoconstrictors to local anesthetic solutions may also increase the risk [20]. Intraoperative positioning also appears to be a risk factor. Patients undergoing surgery in the lithotomy position appear to be at increased risk for neurologic symptoms after either spinal or epidural anesthesia.

Systemic Toxicity

A major cause of adverse reactions to these drugs is high plasma concentration of free unbound medication which may be due to excessive dose, rapid absorption from injection site, diminished tolerance, inadvertent intravascular injection, reduced elimination, or slow metabolic degradation.

The most common toxicities that require immediate countermeasures are related to the central nervous system and the cardiovascular system.

Central Nervous System Effects

Central nervous system toxicity often starts with a change in mentation, followed by perioral paresthesia, a feeling that the subject's whole body is flushing, tinnitus, and generalized seizure as excitation phase followed by depression phase—coma and respiratory and cardiac arrest.

The effects on the CNS may be affected by hypercarbia given that decreased arterial CO_2 pressure also lowers seizure threshold with local anesthetic administration. There is a concomitant increase in cerebral blood flow which allows more local anesthetic to be delivered to the CNS. An increase in intracellular pH leads to ion trapping of the local anesthetic. The acidosis caused by hypercarbia decreases the protein binding of local anesthetics making more drugs available to the CNS. On the other hand, patients receiving CNS depressant drugs such as benzodiazepines or anesthetic drugs will have higher seizure threshold and may not manifest seizure activity before complete CNS depression results.

Cardiovascular System

Toxicity with low doses of local anesthetics may cause hypertension due to vasoconstriction, whereas moderate or high doses result in vasodilatation and decreased SVR.

Local anesthetics have direct effects on the heart and peripheral blood vessels. They block the fast sodium channels in the fast-conducting tissue of Purkinje fibers and ventricles resulting in a decrease rate of depolarization. The effective refractory period and action potential duration are also reduced by local anesthetics. High concentrations can decrease conduction times leading to prolonged PR intervals and widened QRS complexes and even sinus bradycardia/arrest. Ventricular arrhythmias, including fibrillation, are more likely to occur with bupivacaine than lidocaine. Local anesthetics have a dose-dependent negative inotropic effect. This depressant effect is directly proportional to the drugs' relative potency. Patients with acidosis and/or hypoxia are at a greater risk for the cardiac depressant effects of local anesthetics. Cardiotoxicity of local anesthetics can be compared using the CC/CNS dose ratio that is the ratio of the dose causing cardiac collapse (CC) to the dose causing seizure/convulsions. The cardiotoxicity of bupivacaine is unique in that the ratio of the dose required for irreversible cardiovascular collapse (CC) and the dose that will produce CNS toxicity is lower for bupivacaine than other agents. Cardiac resuscitation is more difficult after bupivacaine-induced cardiac arrest. It is important to note that patients under general anesthesia will typically present with cardiotoxicity as the first sign of local anesthetic toxicity given that patients are usually not alert [21]. The very slow reversal of Na^+ channel blockade after a cardiac action potential, which is a hallmark of bupivacaine, is considerably faster with ropivacaine. In addition to these electrical differences, the negative inotropic potency of ropivacaine on isolated cardiac tissue appears to be considerably less than that of

bupivacaine. Both electrical and mechanical differences in the toxic profiles may arise from the selective inhibition of Ca^{2+} currents by bupivacaine [22].

Location of Block

With the same amount of local anesthetic, serum levels can differ depending on location and vascularity of the site. For example, serum levels are highest following intercostals blocks followed by epidural/caudal blocks, followed by brachial plexus and femoral/sciatic nerve blocks, followed by subcutaneous injections. This order parallels the vascular supply of each tissue.

Pregnancy

Bupivacaine has been shown to have increased cardiotoxicity in pregnant women resulting in a decreased CC/CNS dose ratio. The FDA discourages the use of 0.75 % concentration of bupivacaine for obstetrical anesthesia. There have been reports of cardiac arrest with difficult resuscitation or death despite the correct management and treatment [23].

Management of Local Anesthetic Toxicity

The treatment of local anesthetic systemic toxicity (LAST) has unique resuscitative measures. Calling for help early, airway management which includes ventilating with 100 % oxygen, seizure treatment with benzodiazepines, and avoiding propofol in cardiovascular instability are important. In cardiopulmonary instability, basic and advanced cardiac life support (ACLS) is necessary but with prolonged effort and avoiding vasopressin, calcium channel blockers, beta-blockers, or local anesthetics. Most importantly, the patients must be treated with lipid emulsion (20 %) with dosing of 1.5 ml/Kg (lean body mass) bolus over 1 min with continuous infusion of 0.25 mL/kg/min. Bolus may be repeated for persistent cardiovascular collapse and the infusion may be doubled [24].

New Vistas

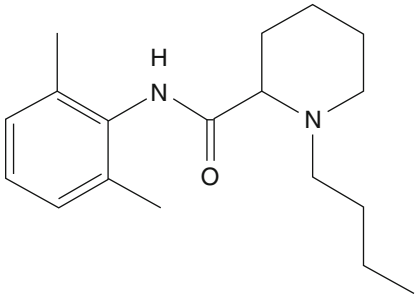
Exparel™ is a novel long-acting liposomal bupivacaine injectable suspension, which was approved by the FDA in Oct. 2011. The technology involves DepoFoam, tiny lipid-based particles containing small discrete water-filled chambers dispersed

through the lipid matrix. The particles are 10–30 μm in diameter and the suspension can be injected through a fine needle. Levels persist for approximately 96 h. Thus, this agent could prove quite beneficial clinically as an ultra long-acting local anesthetic.

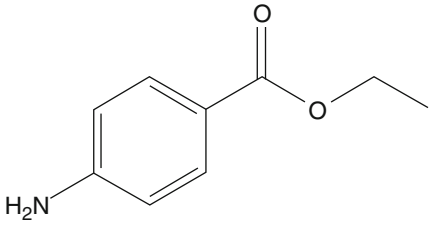
Summary

Many local anesthetics are available commercially and provide a unique option for analgesia and anesthesia for health-care providers. With the onset of ultrasound technology and improvements in pain management, regional anesthetics will continue to rise. Caution must be taken in administering the local anesthetics as both cardiovascular and central nervous system toxicities are a known risk.

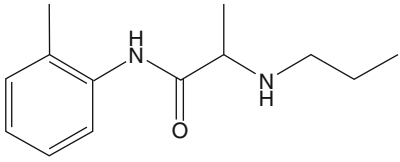
Chemical Structures



Chemical Structure
11.1 Bupivacaine



Chemical Structure
11.2 Benzocaine



Chemical Structure
11.3 Prilocaine

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