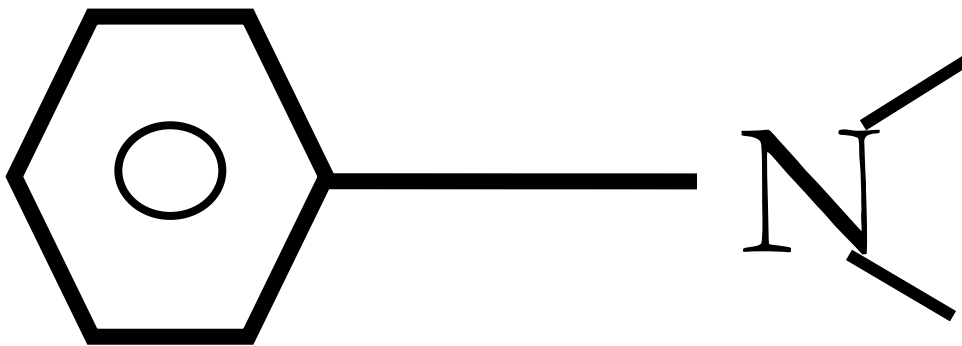# Local Anesthetics

Local anesthetics produce a reversible loss of sensation in a portion of the body. Local anesthetics may be used as the sole form of anesthesia, in combination with general anesthesia, and/or to provide postoperative analgesia.

Indigenous natives of Peru chewed on leaves of Eryroxylon coca, the source of cocaine, to decrease fatigue and promote a feeling of well being. In 1860, Neimann isolates cocaine from coca beans. In 1884, Koller introduced cocaine as a topical anesthetic for the cornea. There were two problems with cocaine, physical dependence and toxicity. In 1905, Einhorn introduced the prototypical ester local anesthetic, procaine. In 1943, Lofgren introduces lidocaine, the prototypical amide local anesthetic. Development of local anesthetics, since the 1950's, has focused on amide local anesthetics. Ester local anesthetics exhibit a number of limitations including instability when in solution, short shelf life, degradation when exposed to high temperatures, and an increased propensity to cause allergic reactions.

Chemistry

The basic chemical structure of a local anesthetic molecule consists of 3 parts:
1. Lipophilic group- an aromatic group, usually an unsaturated benzene ring.
2. Intermediate bond- a hydrocarbon connecting chain, either an ester (-CO-) or amide (-HNC-) linkage. The intermediate bond determines the classification of local anesthetic.
3. Hydrophilic group- a tertiary amine and proton acceptor.

Lipophilic Group	**Intermediate Bond**	**Hydrophilic Group**
Benzene Ring	Ester or Amide Linkage	Tertiary Amine &
	(-CO- ester or –HNC- amide)	Proton Acceptor

Amide and ester local anesthetics follow different paths of metabolism. Ester local anesthetics are more likely to cause an allergic reaction. (See Biotransformation & Excretion).

In the operating room we don't have the opportunity to examine the chemical structure. An easy way to tell the difference between an ester and amide is to determine if the generic name has an "**i"** before the "–caine". This 'trick' will only work with generic name…it will not work with the trade or commercial name. All amide local anesthetics contain an "**i**" in the name. For example, l**i**docaine, mep**i**vacaine, pr**i**locaine, bup**i**vacaine, rop**i**vacaine, and levo-bup**i**vacaine all contain an "**i**" before the "-caine". Esters such as procaine, chloroprocaine, and tetracaine do not contain an "**i**" before the "-caine".

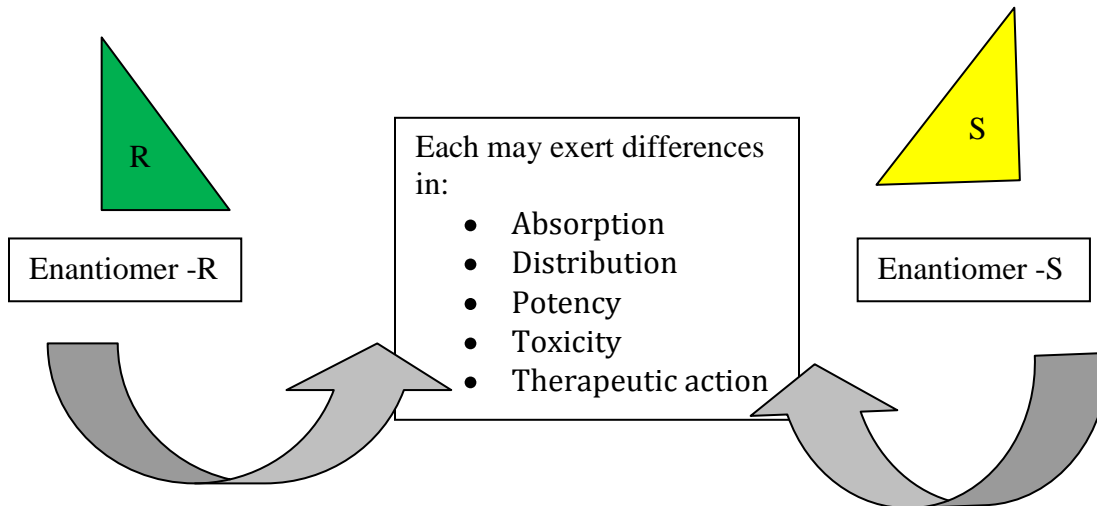| Amides	Esters
Bupivacaine	Benzocaine
Etidocaine	Chloroprocaine
Levobupivacaine	Cocaine
Lidocaine	Procaine
Mepivacaine	Tetracaine
Prilocaine	
Ropivacaine	

Stereoisomerism

Many medications contain chiral molecules which exist as **stereoisomers**. A chiral compound has a carbon atom at the center to which four other compounds are attached. Stereoisomers may be classified as optical, geometric, and conformational. An isomer has the same formula but is structurally different.

Optical isomers (enantiomers) are mirror images of each other. For example each glove to the right has the same shape and are mirror images of each other. They cannot, however be superimposed on one another. With medications each enantiomer may affect the body differently with their physiologic effects. Chiral molecules are asymmetrical and the direction of the configuration helps to categorize the isomer. A molecule which goes to the right is designated with an R for rectus; those that go to the left are designated with a S for sinister. In addition isomers will rotate polarized light in a different direction. **Levorotatory** (L or -) indicates that light is rotated counter clock wise; **dextrorotatory** (D or +) indicates that light is rotated clockwise. Geometric isomers are a group of stereoisomers that are restricted in molecular movement around the chiral carbon atom. Geometric isomers are described as **cis** (which means the same) or Z (zusamman-German equivalent to cis) or with a **trans** or E (entgen-German equivalent to trans) which means opposite. Conformational isomers have the ability to rotate around the chiral carbon to conform to a target receptor.

Up to one-third of all medications administered are stereoisomers. If there are two isomers in equal concentrations it is known as a **racemic mixture**. Racemic epinephrine is an example of an aerosolized medication that is administered to patients who experience stridor in the postoperative period due to supraglottic tissue swelling. Bupivacaine is a racemic preparation of R-bupivacaine and S-bupivacaine. The main issue with administering a racemic preparation is that the patient is receiving two different medications. Receptors are **stereospecific**, which means that they will only allow one stereoisomer to attach to it or **stereoselective**, meaning they prefer one stereoisomer to another. Administering medications that are made up of two different enantiomers may result in different pharmacodynamic and pharmacokinetic effects which include different absorption,

metabolism, excretion, and receptor binding sites. One enantiomer may result in the desired therapeutic effect while the other one may result in undesired effects or be inactive.

R

S

Enantiomer -R

Each may exert differences in:
- Absorption
- Distribution
- Potency
- Toxicity
- Therapeutic action

Enantiomer -S

In general one enantiomer will exhibit greater potency, a better safety profile, and reduced side effects when compared to another. Bupivacaine is a long acting amide local anesthetic that can be associated with significant toxicity issues. S-bupivacaine is almost as potent as the racemic preparation but is less toxic. It takes larger doses of S-bupivacaine to cause cardiac arrest and seizure activity than racemic preparations.   Ropivacaine is a second local anesthetic that is a pure preparation. It contains S-ropivacaine.

Structure Activity Relationships (Potency, Duration, & Onset)

The intrinsic potency, duration, and onset of action for a local anesthetic are dependent upon:
1. Lipophilic-hydrophobic balance
2. Hydrogen ion concentration

Lipophilic-Hydrophobic Balance

The term "lipophilic" means "fat" loving, expressing the tendency of the local anesthetic molecule to bind to membrane lipids. The term "hydrophobic" means fear of water. The lipid membrane is a hydrophobic environment. The term "hydrophobicity" is often used to describe the physiochemical property of local anesthetics. Potency as related to local anesthetics correlates with lipid solubility. In clinical practice, the potency of a local anesthetic is affected by several factors including:

- Hydrogen ion balance
- Fiber size, type, and myelination
- Vasodilator/vasoconstrictor properties (affects rate of vascular uptake)
- Frequency of nerve stimulation
- pH (an acidic environment will antagonize the block)
- Electrolyte concentrations (hypokalemia and hypercalcemia antagonizes blockade)

Duration of action is associated with lipid solubility. Highly lipid soluble local anesthetics generally have a longer duration of action due to decreased clearance by localized blood flow and increased protein binding.

| Local Anesthetic	Potency and Lipid Solubility/Duration of Action
AMIDES	
Bupivacaine/Levo-Bupivacaine	4/4
Etidocaine	4/4
Ropivacaine	4/4
Mepivacaine	2/2
Lidocaine	2/2
Prilocaine	2/2
ESTERS	
Tetracaine	4/3
Cocaine	2/2
Procaine	1/1
Chloroprocaine	1/1

1= least; 4= greatest

Hydrogen Ion Concentration

Local anesthetics are weak bases, containing a positive charge on the tertiary amine at a physiologic pH. Local anesthetics exist in equilibrium between the basic uncharged (non-ionized) form, which is lipid soluble, and the charged (ionized) cationic form, which is water soluble. The measurement pKa expresses the relationship between the non-ionized and ionized concentrations. Specifically, pKa is the pH at which the ionized and non-ionized forms of the local anesthetic are equal.

Non-Ionized Form   **Ionized Form**

**pKa = pH at which ionized and non-ionized forms of local anesthetic are equal.**
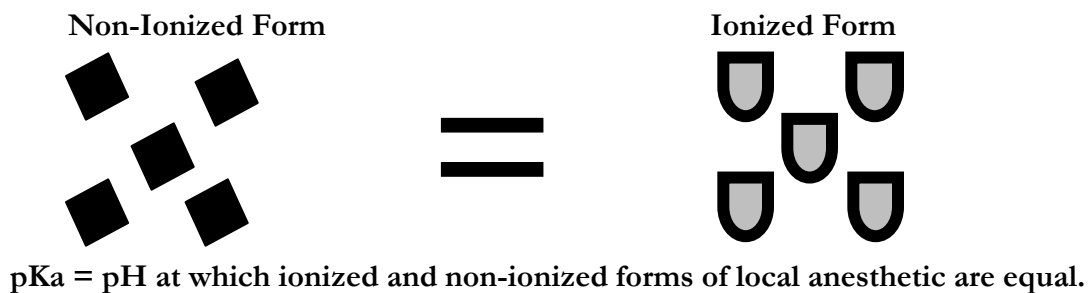
Local anesthetics are weak bases and contain a higher ratio of ionized medication compared to non-ionized. Increasing the concentration of non-ionized local anesthetic will speed onset. In general, local anesthetics with a pKa that approximates physiologic pH have a higher concentration of non-ionized base resulting in a faster onset. On the other hand, a local anesthetic with a pKa that is different from physiologic pH will have more ionized medication which slows onset. For example, the pKa for lidocaine is 7.8 and 8.1 for bupivacaine. Lidocaine is closer to physiologic pH than bupivacaine. Lidocaine has a greater concentration on non-ionized local anesthetic than bupivacaine which results in a faster onset. Non-ionized and ionized portions of local anesthetic solution exert distinct actions. Lipid soluble, non-ionized form of the local anesthetic penetrates the neural sheath and membrane. In the cell, the non-ionized and ionized forms equilibrate. The ionized form of the

local anesthetic binds with the sodium channel. Once "bound" to the sodium channel, impulses are not propagated along the nerve.

Ionized　　　　**Non-ionized penetrates the neural sheath/membrane**

Lipid
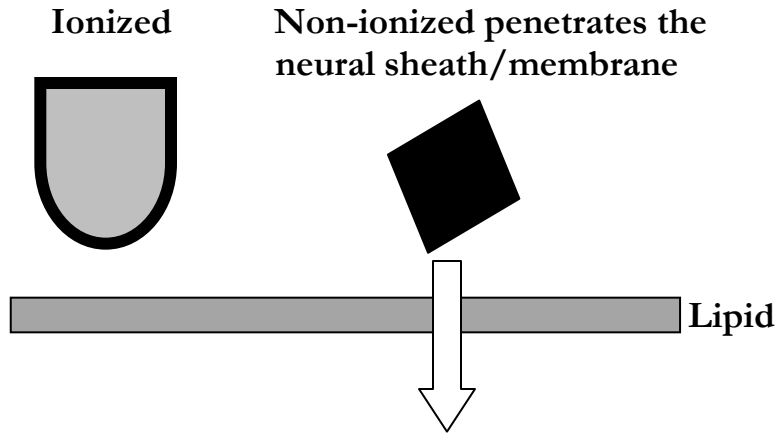
Ionized- binds with the sodium channel

Ionized form of local anesthetic molecule

Na+ Channel
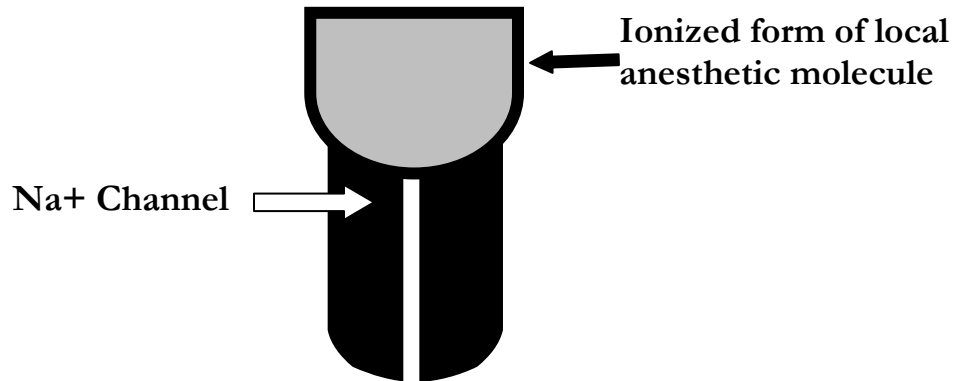
Local Anesthetic	pKa
AMIDES	
Bupivacaine and levo-Bupivacaine	8.1
Ropivacaine	8.1
Lidocaine	7.8
Prilocaine	7.8
Etidocaine	7.7
Mepivacaine	7.6
ESTERS	
Chloroprocaine	9.0
Procaine	8.9
Cocaine	8.7
Tetracaine	8.2

Clinically, onset of action is not the same for all local anesthetics with the same pKa. This is due to the intrinsic ability of the local anesthetic to diffuse through connective tissue. Local anesthetics with a pKa closest to the physiological pH generally have a higher concentration of non-ionized molecules and a more rapid onset. Two notable exceptions are chloroprocaine and benzocaine. Chloroprocaine has a high pKa and rapid onset. Benzocaine does not exist in an ionized form and exerts its effects by alternate mechanisms.

Clinical Implications of Ionized and Non-ionized Forms of Local Anesthetic

Local anesthetics are prepared as a water soluble hydrochloride salt and generally have a pH of 5-6. If the commercial preparation contains epinephrine, the solution must be acidic to create a stable environment. The corresponding pH is in the range of 3-4. Commercial preparations with epinephrine have less free base, slowing the onset of action. To enhance clinical onset, carbonated solutions of epinephrine containing local anesthetics have been used instead of HCL solutions. Alternatively, adding sodium bicarbonate to commercial preparations of epinephrine containing local anesthetic solutions can hasten the onset. One (1) ml of 8.4% sodium bicarbonate should be added to each 10 ml of lidocaine or mepivacaine, and 0.1 ml of 8.4% of sodium bicarbonate should be added to each 10 ml of bupivacaine. Increasing the volume of sodium bicarbonate added the local anesthetic preparation may lead to precipitation. Altering the pH to a more basic solution will increase the amount of non-ionized compared to ionized which will speed onset. Sodium bicarbonate increases the amount of free base, increases onset, improves the quality of the block, and decreases pain associated with subcutaneous infiltration.
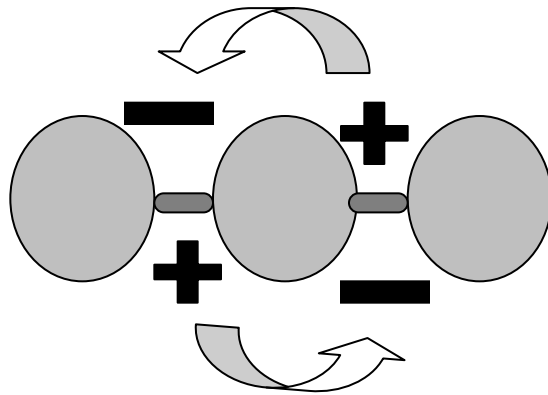
Peripheral Nerve Anatomy

**Axolemma**- the peripheral nerve axon cell membrane.

Non-myelinated nerves- contain axons within a single Schwann cell (i.e. autonomic postganglionic efferent and nociceptive afferent C fibers).

Large motor and sensory fibers are enclosed in many layers of myelin.

Myelin insulates the axolemma and speeds conduction to the nodes of Ranvier. The nodes of Ranvier are interruptions in the myelin, allowing current regeneration. High concentrations of Na+ channels are located at the nodes of Ranvier.

Non-myelinated fibers have Na+ channels distributed along the axon.
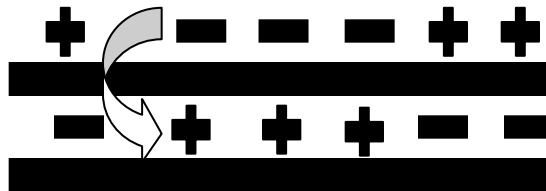
A peripheral nerve contains several axon bundles called fascicles.
Endoneurium is the connective tissue that covers an individual nerve.
Perineurium is the connective tissue that covers each fascicle.
Epinerium is the connective tissue covering the entire nerve.

Schematic Illustration of Nerve

Epineurium

Perineurium

Endoneurium
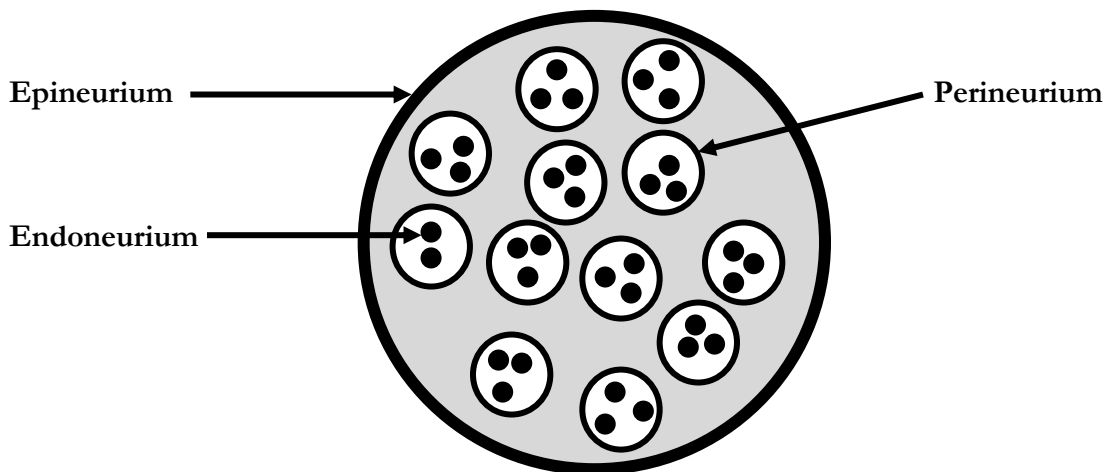
Nerve Conduction Physiology

The neural membrane contains a voltage difference of +60 mV (inner) to -90 mV (outer). At rest the neural membrane is impermeable to Na+ ions, and selectively permeable to K+ ions. The Na+/K+ pump maintains the ion gradient. The K+ to Na+ gradient is constant at 30:1. Within the cell, the concentration of K+ is kept at 30, and outside the cell it is maintained at 1. Sodium, on the other hand, is at higher concentrations outside the cell.

At Rest
Outside Cell

-90 mV   **K+ concentration low; Na+ concentration high**

Neural Membrane

+ 60 mV   **K+ concentration high; Na+ concentration low**

Inside Cell

During an action potential, the nerve membrane switches its permeability from K+ to Na+, changing the membrane potential from -90 to +60 mV (negative to positive) and back again.

Action Potential
Outside Cell

Neural Membrane   **+60 mV**   **Na+**

-90 mV   **K+**

Inside Cell
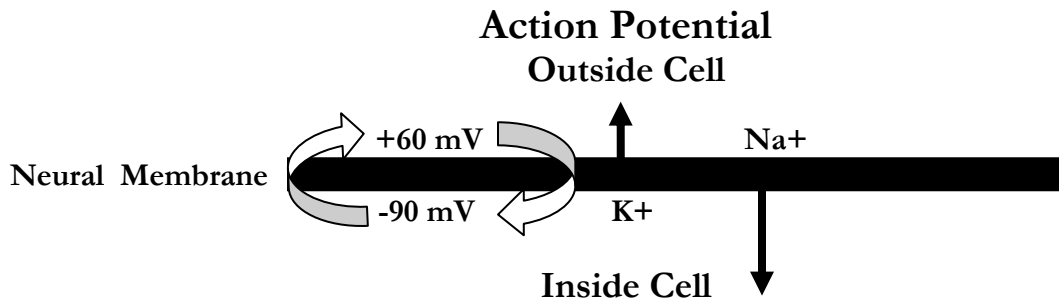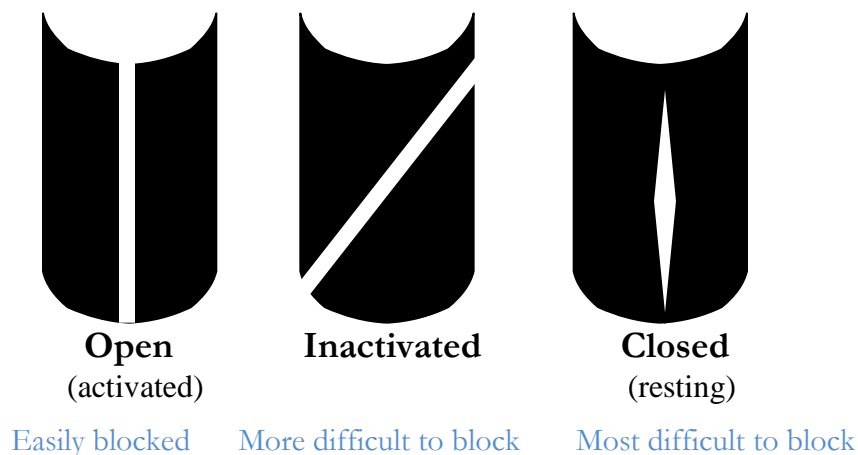
Local anesthetics produce a conduction block of neural impulses, preventing the passage of Na+ through Na+ channels.

Local Anesthetic Molecule
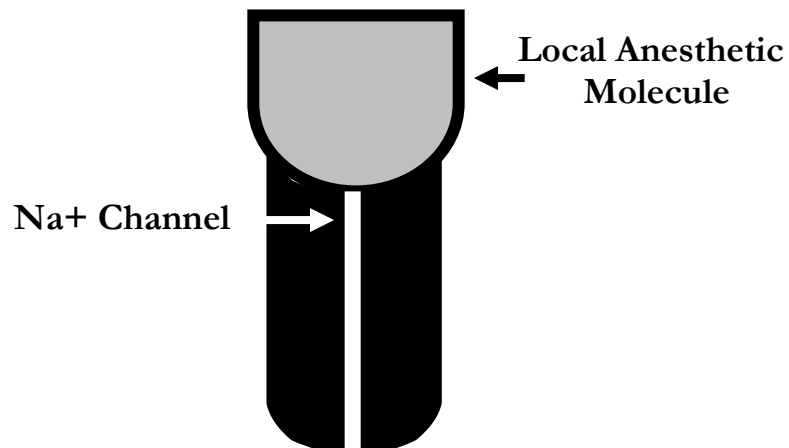
Na+ Channel

Local anesthetics DO NOT alter the resting membrane potential. The Na+ channel acts as a receptor for local anesthetic molecules. Local anesthetics are stereospecific. Their action is dependent on the conformational state of the Na+ channel. Local anesthetics ability to bind to sodium channels is known as a state-dependent block". Local anesthetics bind more readily to the Na+ channel during depolarization (when it is open or activated). The open sodium channel is the primary binding site of local anesthetics. This is followed by an inactivated state. Local anesthetics may bind during the resting state but not as readily as during the "open" or "inactivated" state.

Conformational State of Na+ Channel

Open	Inactivated	Closed
(activated)		(resting)
Easily blocked	More difficult to block	Most difficult to block

In the "inactivated" state, local anesthetics stabilize the Na+ channel. Local anesthetic molecules may bind within the Na+ channel as well as block the external opening. This action prevents permeability to Na+, slowing the rate of depolarization. The rate of depolarization is slowed; threshold potential is not met or propagated along the nerve membrane. Repeated depolarization increases the number of local anesthetic molecules bound to Na+ channels by increasing the number of available binding sites. Local anesthetic disassociation from inactivated channels occurs at a slower rate compared to resting channels.

Sodium channels can be divided into those that are tetrodotoxin resistant and tetrodotoxin sensitive. Sensory neurons generally contain tetrodotoxin sensitive sodium channels whereas small dorasal root ganglions contain more resistant sodium channels.

Fiber Types

There are several classifications of nerve fibers. The classification of a nerve fiber impacts its sensitivity to local anesthetics. The order of susceptibility to blockade by fiber type is as follows: (least susceptible to most susceptible) small myelinated fibers (Aα motor) < Aα type Ia; Aα type Ib; Aβ type II; Aγ < Aδ sensory fibers < small, non-myelinated C fibers, and partially myelinated B fibers.

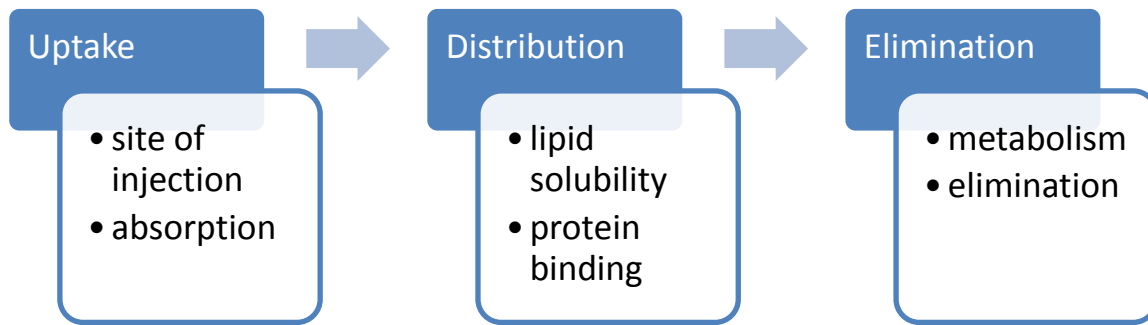| Fiber Type	Function	Diameter (mm)	Speed of Conduction	Local Anesthetic Sensitivity*	Myelination
Aα	Motor	12-20	Fast	1	Yes
Aα	Proprioception	12-20	Fast	2	Yes
Aα	Proprioception	12-30	Fast	2	Yes
Aβ	Touch Pressure/Proprioception	5-12	Medium	2	Yes
Aγ	Motor	3-6	Medium-Slow	2	Yes
Aδ	Pain Cold Temperature Touch	2-5	Medium-Slow	3	Yes
B	Preganglionic autonomic fibers	<3	Medium-Slow	4	Some
C (dorsal root)	Pain Warm and Cold Touch	0.4-1.2	Slow	4	No
C (sympathetic)	Postganglionic sympathetic fibers	0.3-1.3	Slow	4	No

(* local anesthetic sensitivity= 1 is the least sensitive and 4 is most sensitive)

Summary of Impulse Blockade by Local Anesthetics

1. Local anesthetic is deposited near a nerve. A portion of the local anesthetic is removed due to tissue binding and circulation. If the local anesthetic is an ester, a portion of the deposited local anesthetic will be removed by local hydrolysis, in addition to tissue binding and circulation. The remaining local anesthetic penetrates the nerve sheath.
2. Local anesthetic penetrates the axon membranes and axoplasm. This step is dependent on pKa and lipophilicity.
3. Local anesthetic binds to Na+ channels preventing their opening by inhibiting conformational changes resulting in activation. Local anesthetics may also bind to the channel pore and block the passage of Na+.
4. During onset, impulse blockade is incomplete. Partially blocked fibers are inhibited by repetitive stimulation. The reverse is true during recovery.
5. The primary route for local anesthetics is the hydrophobic route, within the axon membrane.
6. Clinical onset of blockade is due to the slow diffusion of local anesthetic molecules into the nerve, NOT by binding to ion channels and inhibition of impulse propagation, which occurs at a faster rate. Recovery occurs in reverse.

Pharmacokinetics

Pharmacokinetics involves the medication/body interaction. It is how the body handles medication. Principles of pharmacokinetics include: absorption, distribution, metabolism, and elimination.

Uptake		Distribution		Elimination
• site of injection • absorption	→	• lipid solubility • protein binding	→	• metabolism • elimination

Local anesthetic blood concentration is determined by:
- Amount of local anesthetic injected
- Absorption rate
- Site of injection
- Rate of tissue distribution
- Rate of biotransformation
- Excretion rate

Patient related factors include:
- Age
- Cardiovascular status
- Hepatic function

Systemic Absorption of Local Anesthetics
Systemic absorption of local anesthetics is determined by:
- Site of injection
- Dose
- Addition of vasoconstrictor
- Pharmacologic profile of the local anesthetic

1. Site of Injection
Site of injection impacts blood levels of local anesthetic. Areas of high vascularity result in greater uptake and higher blood concentrations. The uptake of local anesthetic from greatest to least is as follows:

IV> tracheal> intercostal> caudal> paracervical> epidural> brachial> sciatic> subcutaneous

Uptake of Local Anesthetics Based on Regional Anesthetic Technique

Result in Highest Blood Concentrations
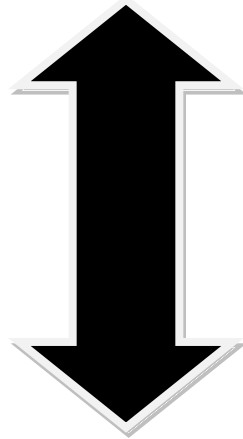
Intravenous
Tracheal
Intercostal
Caudal
Paracervical
Epidural
Brachial
Sciatic
Subcutaneous

Lower Blood Concentrations of Local Anesthetic

Clinically, the site of injection plays an important role in toxicity. For example, 400 mg of plain lidocaine in the intercostal space may lead to peak blood concentrations of 7 mcg/ml. This may result in CNS toxicity. In contrast, 400 mg of plain lidocaine in the brachial plexus will yield blood levels of 3 mcg/ml, which is not toxic.

Toxicity associated signs and symptoms may vary among local anesthetics. For example, with lidocaine there is a larger disparity in blood concentrations required to cause CNS signs and symptoms compared to concentrations that result in cardiovascular collapse. With bupivacaine there is a small difference in the blood concentrations that may result in CNS signs and symptoms and concentrations that result in cardiovascular collapse. Often seizures occur at the same time as cardiovascular collapse. Ropivacaine is similar to bupivacaine with respect to onset and duration. However, blood concentrations of ropivacaine required to cause cardiovascular collapse are much higher than bupivacaine. Ropivacaine has a larger margin of safety. In addition, metabolism plays a role in toxicity. Amides have a high rate of first pass metabolism as the local anesthetic passes through the liver. Slow absorption from tissue is less likely to result in toxicity. Toxicity is often the result of intravenous/intra-arterial injection or overdose.

Local Anesthetic Toxicity Lidocaine

Signs & symptoms based on increasing blood concentrations of lidocaine.
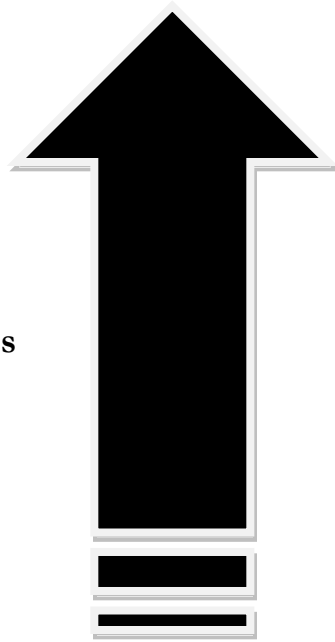
Cardiac depression/arrest

Respiratory arrest

Seizures

Dizziness, ringing of ears, 'funny' taste in the mouth.

2. Dose

Peak blood concentrations of local anesthetics correspond proportionally to the total dose administered.

3. Vasoconstrictor

Epinephrine, in concentrations of 5 mcg/ml, is commonly used to decrease the absorption of local anesthetics. A 5 mcg/ml (1:200,000) dose of epinephrine will significantly reduce the peak blood levels of lidocaine and mepivacaine regardless of the site of administration. Epinephrine does not affect the vascular absorption of etidocaine and bupivacaine in the epidural space. However, the addition of epinephrine does significantly reduce the vascular absorption of etidocaine and bupivacaine when utilized for peripheral nerve blocks. Benefits of decreased absorption include increased neuronal uptake, enhanced quality of analgesia/anesthesia, prolonged duration of action, and decreased risk of toxicity.

A concentration of 1:200,000 (5 mcg/ml) is commonly used for peripheral nerve blocks to reduce vascular absorption. To add epinephrine to local anesthetic solutions use a 1mg/ml (1:1000) ampoule of epinephrine. Take the total volume of local anesthetic, divide it in half, and move the decimal point two places to the left. For example, 40 ml of 1% lidocaine, divide 40 by 2 and 20 is the result. Next, move the decimal point two places to the left. The result is 0.20. This is the amount of epinephrine added to the local anesthetic solution to yield a 1:200,000 concentration. To check the calculation, multiply 5 mcg/ml by 40 ml, which equals 200 mcg. It is important to always check the concentration of epinephrine and the total dose added to the local anesthetic.

A second technique for adding epinephrine to local anesthetic preparations is detailed below:
- 1:200,000 epinephrine concentration would equal 5 mcg/ml.

- Dilute epinephrine using a 10 ml syringe. Draw up 1 ml of 1:1000 epinephrine (1 mg per ml) and 9 ml of normal saline.
- Mix it by tilting the syringe back and forth.
- The concentration of epinephrine is now 100 mcg per ml.
- Add epinephrine to the local anesthetic solution (see table below).

1:200,000 Epinephrine Concentration	
Volume of Local Anesthetic	Amount of Epinephrine Added to Local Anesthetic Solution
20 ml	100 mcg of epinephrine
30 ml	150 mcg of epinephrine
40 ml	200 mcg of epinephrine
50 ml	250 mcg of epinephrine

- Always label the syringe of epinephrine. Once the epinephrine is added to the local anesthetic, discard what remains. Epinephrine can be lethal and should be discarded to avoid inadvertent administration.
- Epinephrine containing local anesthetics should never be injected into end organs such as ears, nose, penis, fingers, or toes. Epinephrine may cause vasoconstriction and subsequent necrosis of tissue.

4. Pharmacologic Profile

Individual local anesthetics exhibit different rates of absorption. For example, it has been found that during brachial plexus blockade, lidocaine is absorbed faster than prilocaine, and bupivacaine is absorbed more rapidly than etidocaine. In general, local anesthetics that are highly tissue bound are absorbed at a slower rate. In addition, absorption is dependent on the individual local anesthetics intrinsic ability to cause vasodilatation.

Distribution of Local Anesthetics

A two compartment model describes the systemic distribution of local anesthetics. The rapid disappearance phase (α phase) is related to uptake by rapidly equilibrating tissue (tissue with high vascular perfusion which include the brain, lung, liver, kidney, and heart). The slow phase of disappearance (β phase) is the function of the individual local anesthetics distribution, biotransformation, and excretion.

Local anesthetics are distributed to all tissues. Higher concentrations of local anesthetics are found in highly perfused organs compared to tissues that receive lower rates of perfusion. The pulmonary system is responsible for extraction of local anesthetics. As local anesthetics are transported through the pulmonary vasculature, levels are greatly reduced. The largest reservoir for local anesthetics is the skeletal muscle.

Biotransformation and Excretion of Local Anesthetics

The metabolism of local anesthetics is dependent upon their classification: ester vs. amide. Ester local anesthetics undergo extensive hydrolysis in the plasma by pseudocholinesterase enzymes (plasma cholinesterase or butyrylcholinesterase). Ester hydrolysis is rapid, resulting in water soluble

metabolites which are excreted in the urine. The ester that is an exception is cocaine. In addition to ester hydrolysis cocaine is partially metabolized in the liver (N-methylation). Patients with pseudocholinesterase deficiency are at risk for toxicity (genetic or liver disease). This is due to slowed metabolism and accumulation of the ester local anesthetic. Procaine and benzocaine are metabolized to p-aminobenzoic acid (PABA), which has been associated with allergic reactions. Benzocaine may result in methemoglobinemia. When ester local anesthetics are placed in the CSF, metabolism does not occur until there has been vascular absorption of the local anesthetic. CSF does not contain esterase enzymes.

Amide local anesthetics are metabolized primarily by microsomal P-450 enzymes in the liver (N-dealkylation and hydroxylation) and, to a lesser extent, in other tissues. The rate of metabolism among amides varies.

prilocaine> lidocaine> mepivacaine> ropivacaine> bupivacaine.

Prilocaine metabolites include o-toluidine derivatives, which can accumulate after large doses (>10 mg/kg), resulting in the conversion of hemoglobin to methemoglobinemia. Treatment for methemoglobinemia includes the administration of methylene blue. Methylene blue is generally available in a 1% solution. 1-2 mg/kg should be administered over 5 minutes. Methylene blue reduces methemoglobin to hemoglobin.

The excretion of amide local anesthetics occurs in the kidneys. Less than 5% of the unchanged medication is excreted by the kidneys.

Patient Alterations in the Pharmacokinetics of Local Anesthetics

Age is one factor that alters the pharmacokinetics of local anesthetics. Changes in half life have been demonstrated for the elderly and newborns. In both populations, lidocaine has been found to have an increased half life. Newborns have an immature hepatic enzyme system, whereas the elderly have decreased hepatic blood flow.   The second factor that affects the pharmacokinetics of local anesthetics includes any disease process (i.e. liver disease or congestive heart failure) that diminishes hepatic blood flow or impairs the livers ability to produce enzymes. This may result in elevated levels of amide local anesthetics in these patients compared to patients with normal liver function.

Clinical Pharmacology

General Considerations

General considerations related to local anesthetics include the following:

- Anesthetic potency
- Onset of action
- Duration of action
- Differential sensory/motor blockade

Potency, onset, and duration were covered earlier under structure activity relationships.   For completeness they will be briefly covered under clinical pharmacology.

Anesthetic Potency

The primary factor related to potency is the hydrophobicity (lipid solubility) of the local anesthetic. Local anesthetics penetrate the nerve membrane and bind to Na+ channels, which are hydrophobic. Additional factors include:

- Fiber size, type, and myelination
- Hydrogen ion balance
- Vasodilator/vasoconstrictor properties (affects the rate of vascular uptake)
- Frequency of nerve stimulation
- pH (acidic environment will antagonize the block)
- Electrolyte concentrations (hypokalemia and hypercalcemia antagonizes blockade).

Onset of Action

In the individual nerve, onset is related to the unique physiochemical property of the local anesthetic. Clinically, the onset of action is related to pKa, dose, and concentration.

- pKa – when pKa approximates the physiologic pH a higher concentration of non-ionized base is available, increasing onset of action.
- Dose- the higher the dose of local anesthetic administered, the faster the onset.
- Concentration- higher concentrations of local anesthetic will result in a more rapid onset.

Duration of Action

Duration of action is dependent on individual local anesthetic characteristics. Local anesthetics are classified as follows:

- Short acting: procaine and chloroprocaine
- Moderate acting: lidocaine, mepivacaine, prilocaine
- Long acting: tetracaine, bupivacaine, etidocaine, ropivacaine, levobupivacaine

One of the dominant factors related to the duration of action is protein binding. Since local anesthetic molecules bind to a protein receptor, the greater the affinity of the local anesthetic molecule to bind to a protein and subsequently the longer it will remain bound extending the duration of action.

Duration of action is influenced by peripheral vascular effects that local anesthetics exhibit. Local anesthetics exhibit a biphasic effect on vasculature smooth muscle. At low, sub-clinical doses, vasoconstriction is noted. With larger, clinically relevant doses, vasodilatation is seen. The degree of vasodilatation varies among individual local anesthetics. For example, lidocaine> mepivacaine> prilocaine. The effect of local anesthetics on vascular tone and regional blood flow is complex and dependant on the following:

- Concentration
- Time
- Type of vascular bed

Intrinsic Effect of Local Anesthetic on Vasculature

Lidocaine   Bupivacaine   Mepivacaine   Ropivacaine

Vasodilatation   **Vasoconstriction**
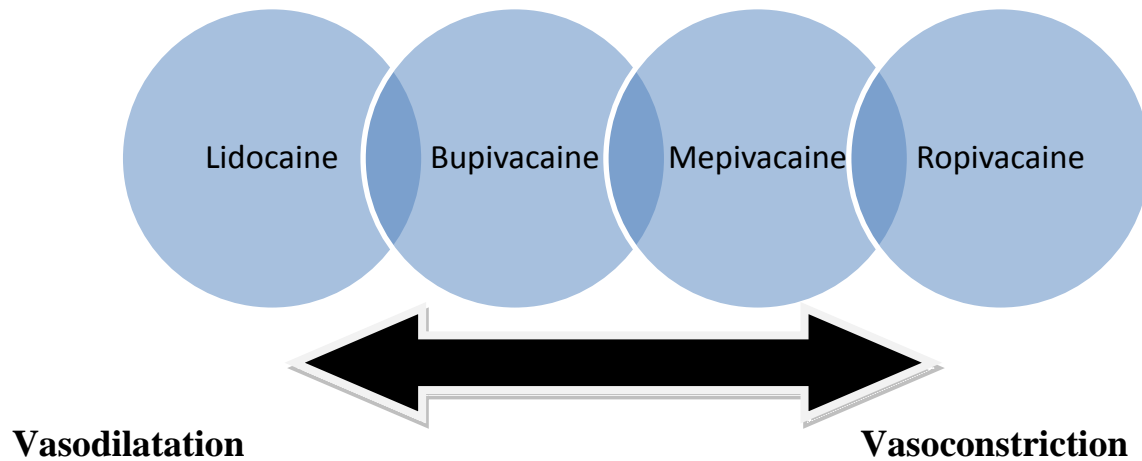
Intrinsic effect of individual local anesthetics do not have a clinically significant effect.

Ropivacaine is unique among local anesthetics since it exhibits a cutaneous vasoconstrictive effect at clinically relevant doses.

Differential Sensory/Motor Blockade

Differential blockade refers to the ability of a local anesthetic to block noxious stimuli but still retain motor blockade. Classically this has been attributed to smaller neuronal axons being more sensitive to local anesthetics than others. This phenomenon may be more complex than previously thought and may include anatomical factors as well as sodium and potassium sensitivities to various local anesthetics. Local anesthetics have the ability to produce varying degrees of inhibition for sensory and motor activity. For example, bupivacaine and etidocaine are both potent, long acting local anesthetics. Bupivacaine exhibits a more potent sensory than motor block. Etidocaine exhibits an equally effective sensory and motor block. Ropivacaine, on the other hand, exhibits a potent sensory block similar to bupivacaine but motor blockade appears less intense.

Factors Affecting Local Anesthetic Activity Clinically

Dose

An increase in the dose of a local anesthetic will increase the likelihood of a successful block by producing a solid and long lasting anesthetic while decreasing the time to onset. An increase in the volume of local anesthetic using the same dose of local anesthetic does not appear to be beneficial in the clinical setting with the exception of the spread associated with epidural anesthesia.

Addition of Vasoconstrictors

Epinephrine is the most commonly used vasoconstrictor. The usual dose and concentration is 5 mcg/ml or 1:200:000. Norepinephrine and phenylephrine have been used as vasoconstrictors but do not exhibit properties that make them superior to epinephrine. Epinephrine acts to decrease

vascular absorption, reduces blood concentration of local anesthetics, and decreases the risk of toxicity thus allowing more local anesthetic molecules to reach the nerve membrane. As more molecules reach the nerve membrane, there is an increase in the depth and duration of local anesthetic blockade. Epinephrine prolongs the duration of blockade for most short to moderate acting local anesthetics. The addition of epinephrine for neuraxial blockade has the added benefit of activating endogenous analgesic mechanisms through α-Adrenergic receptors. This may increase the intensity of analgesic action. The addition of vasoconstrictors is controversial. Some advocate that vasoconstrictors may result in nerve injury due to decreased blood flow. Epinephrine containing local anesthetics should never be injected into end organs such as ears, nose, penis, fingers, or toes. Epinephrine may cause vasoconstriction and subsequent necrosis of tissue.

Site of Injection

The anatomical location of blockade influences onset and duration. Location affects the rate of diffusion, vascular absorption, and the amount of local anesthetic administered. Subarachnoid blockade exhibits the most rapid onset and shortest duration of action. Rapid onset, within the subarachnoid space, occurs because nerve roots are not covered with a sheath. The short duration of action is related to the small dose and volume of local anesthetic used to produce anesthesia. Brachial plexus blockade, in contrast, has slower onset and longer duration of action. Local anesthetics are deposited in the sheath around the brachial plexus. Diffusion must take place before reaching the site of action. The long duration of action is related to slow vascular absorption, large doses, and increased exposure of neural tissue to local anesthetics.

Carbonation and pH adjustment

In the isolated nerve, adding carbon dioxide to the local anesthetic solution accelerates the onset on blockade. This is a result of an increase in the base from of the local anesthetic, direct effect of CO_2 on the nerve, and a decrease in the local pH. Clinically results are mixed. Sodium bicarbonate may also accelerate the onset of action. The addition of bicarbonate increases the pH, which in turn, increases the amount of local anesthetic in the uncharged base form. This theoretically accelerates the rate of diffusion across the sheath and membrane, resulting in a faster onset. Controversy exists concerning the clinical utility of pH adjustment. Studies remain ambiguous concerning the use of sodium bicarbonate to improve the speed of local anesthetic induced anesthesia.

Mixtures of Local Anesthetics

Clinicians occasionally will combine local anesthetics to achieve quick onset and long duration. Often the clinician will combine a local anesthetic with a fast onset with a local anesthetic that has a long duration of action to achieve this goal. Clinical trials have yielded mixed results. Chloroprocaine and bupivacaine, in the brachial plexus region, have achieved a quick onset/prolonged duration. However, when used for epidural anesthesia it was found that the duration of action was shorter than if bupivacaine was administered alone. Clinically there are few advantages to this technique. It should be noted that when mixing local anesthetics the risk of toxicity remains. Care should be exercised not to exceed the maximum dose. Toxicities of local anesthetics are not independent, but additive! A solution containing 50% of the toxic dose of local anesthetic A, and 50% of the toxic dose of local anesthetic B, will have the same implications as 100% of the toxic dose of either local anesthetic alone.

Pregnancy

Hormonal changes during pregnancy are primarily responsible for the enhanced potency of local anesthetics. Mechanical factors such as dilated epidural veins, which decrease the volume of the epidural or subarachnoid space, may play a minor role in later stages of pregnancy. The spread and depth of epidural/spinal anesthesia is greater in the pregnant patient when compared to the patient who is not pregnant. It has been found that the spread of local anesthetics are more extensive with epidural anesthesia as early as the first trimester. There is a correlation between progesterone levels and the mg per segment requirement of lidocaine required for the parturient. Based on current research, the dose of local anesthetics should be reduced for the pregnant patient by 30%, regardless of the trimester of pregnancy.

Medication Interactions with Local Anesthetics

Ester Local Anesthetics	Succinylcholine- may potentiate the effects since both are dependent on pseudocholinesterase for metabolism.
Ester Local Anesthetics	Cholinesterase inhibitors such as neostigmine and pyridostigmine can lead to a decrease in the metabolism of ester local anesthetics.
Ester Local Anesthetics	Decreased pseudocholinesterase activity during pregnancy and postpartum period.
Local Anesthetics in General	Opioids and alpha adrenergic agonists potentiate the analgesic effects of local anesthetics.
Local Anesthetics in General	Potentiate the effects of non-depolarizing muscle relaxant blockade.
Chloroprocaine (epidural)	May interfere with the analgesic effects of subarachnoid opioids.
Lidocaine	Cimetidine and propranolol decrease hepatic blood flow and lidocaine clearance. This acts to increase the risk of systemic toxicity.

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