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Local Anesthetics

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Local anesthetics are administered to prevent or treat acute perioperative pain. They are also utilized in the diagnosis and treatment of cancer related, chronic, and inflammatory pain disorders. The traditional mechanism of action of local anesthetics is via blockade of axonal action potential generation or propagation by prevention of voltage-gated sodium (Na^+) channel (VGSC) conductance that mediates these action potentials. Additionally, local anesthetics also interact with calcium (Ca^{2+}) signaling G protein coupled receptors (GPCRs), and may mediate their anti-inflammatory actions.

The clinical activity of local anesthetics is largely determined by their chemical structure and physicochemical properties. Amino ester local anesthetics are metabolized by plasma cholinesterases, and aminoamides are metabolized in the liver. The potency of local anesthetics correlates with increasing molecular weight, which confers increased lipid solubility and protein binding, both of which increase the duration of action, but slow the onset of conduction block. Local anesthetics exist in a dynamic equilibrium between the neutral lipid soluble form (which facilitates penetration of the axonal lipid bilayer membrane to gain access to the intracellular receptor within the VGSC) and the ionized hydrophilic form (which is the active form once intracellular). The factors that govern the rate and extent of local anesthetic systemic absorption are the physicochemical properties of the local anesthetic, the total mass of drug administered, and site of injection. Epinephrine is the most widely used local anesthetic additive, and its vasoconstrictive properties prolong the duration of action of local anesthetics by decreasing vascular absorption.

Local anesthetics have the potential to cause direct toxicity of nerves, but this is a rare occurrence in clinical application. The potential systemic toxic effects of local anesthetics include methemoglobinemia (primarily due to benzocaine and the metabolite of prilocaine, *o*-toluidine), seizures, and malignant ventricular dysrhythmias with cardiovascular collapse. True allergic reactions to local anesthetics are rare, but may be associated with the metabolites of the aminoester local anesthetics or preservatives in the local anesthetic solutions.

Mechanisms of actions of local anesthetics Functional anatomy of axons

Action potentials are the mechanism by which information is transmitted between electrically excitable cells of the central and peripheral nervous systems. VGSCs are integral membrane proteins that are responsible for initiation, propagation, and oscillation of electrical impulses in electrically excitable tissues [1]. Local anesthetics are most often administered inclose proximity to nerves within the peripheral and central nervous systems. Peripheral nerves are mixed nerves containing both afferent and efferent fibers that may be myelinated or unmyelinated. Each peripheral nerve axon possesses its own cell membrane, which contains the VGSC, responsible for neural conduction. Nonmyelinated nerve fibers contain multiple axons that are simultaneously encased by a single Schwann-cell sheath. VGSCs are distributed all along the axon of nonmyelinated nerve fibers. Propagation of action potentials in nonmyelinated axons occurs when Na^+ currents enter the axoplasm generating an action potential, which then depolarizes the adjacent membrane. In contrast, myelinated nerve fibers are segmentally encased by multiple layers of myelin formed from the plasma.

membranes of specialized Schwann cells that wrap around a single axon. The myelin sheath may account for greater than 50% of the thickness of myelinated nerve fibers. Periodic interruptions in the myelin sheath (nodes of Ranvier) are where VGSCs are concentrated along the axons of myelinated nerve fibers. The presence of myelin significantly increases the speed of axonal conduction by electrically insulating the cell mem- brane from the surrounding conducting ionic medium. In myelinated axons, Na^+ currents are restricted to enter the axoplasm through the nodes of Ranvier, allowing action potential propagation to jump from one Ranvier node to the next (saltatory conduction). In general, increasing myelination and nerve-fiber diameter are associated with increased conduction velocity. The presence of myelin increases conduction velocity via saltatory conduction, and the increased nerve diameter increases conduction velocity via improved cable conduction properties.

The nerve fiber is the basic structural and functional unit of peripheral nerves. A typical peripheral nerve is composed of several axon bundles, or fascicles. A loose connective tissue sheath called the endoneurium, composed of nonneural glial cells, encases each axon. A second connective tissue sheath, the perineurium, composed of several alternating layers of flattened cells and collagen, encases individual fascicles. Lastly, the entire peripheral nerve, consisting of multiple fascicles, is encased in a moderately dense connective tissue sheath known as the epineurium. The presence of these multiple layers serves to protect the peripheral nerve, but also presents a significant barrier to local anesthetics reaching their intended site of action within the axonal cell membranes. For example, a rat sciatic nerve model demonstrated that only 1.6% of an administered dose of local anesthetic penetrates in to the nerve to achieve a functional block [2]. A classification of peripheral nerves based on size, presence of myelin, speed of conduction, and physiological function is presented in (Table 1).

Table 1. Classification of nerve fibers

Classification	Diameter (μ)	Myelin	Conduction velocity ($m\ s^{-1}$)	Location	Function
Aα	6–22	þ	30–120	Efferent to muscles	Motor
Aβ	6–22	þ	30–120	Afferent from skin and joints	Tactile and proprioception
Aγ	3–6	þ	15–35	Efferent to muscle spindle	Muscle tone
Aδ	1–4	þ	5–25	Afferent sensory nerve	Pain, cold temperature, and touch
B	< 3	þ	3–15	Preganglionic sympathetic	Autonomic function
C	0.3–1.3	–	0.7–1.3	Postganglionic sympathetic	Autonomic function, warm temperature, Pain, and touch

Data from Stranding [3].

Molecular mechanisms of local anesthetic action

Local anesthetics inhibit neuronal conduction by directly binding to and inhibiting the ability of VGSCs to conduct the inward Na^+ current that mediates the rapid depolarizing phase of the action potential [4]. The inhibition results from local anesthetic binding at a receptor site in the channel's inner pore, accessible from the axoplasmic opening. Binding of the local anesthetic is a dynamic process characterized by differing affinities for the receptor site based on conformational changes of the VGSC, induced by temporal changes in the membrane potential. At resting membrane potentials, VGSCs predominantly exist in a resting (closed) conformation. When a threshold depolarization is reached, VGSCs are suddenly activated (opened), allowing the inward Na^+ current to further depolarize the membrane potential, leading to further VGSC opening until the equilibrium potential for Na^+ is reached. Following activation of VGSC and initiation of the action potential, the VGSCs rapidly inactivate in orderto terminate the action potential and return the membrane to its resting potential. Within a few milliseconds of activation, the VGSCs spontaneously undergo a conformational change to an inactivated state, whereupon the inward Na^+ current ceases. Subsequent depolarizations cannot open the VGSC from its inactivated state. The VGSC must undergo a conformational change back to the resting closed state before it is reprimed to open again. Almost simultaneously, voltage-gated K^+ channels are activated and open in response to depolarization, but with a slight delay and at a slower rate than the VGSCs. The inactivation of VGSCs in combination with outward K^+ current via the activated K^+ channels results in membrane repolarization to the negative resting membrane potential. During the process of repolarization, the inactivated Na^+ channels and activated K^+ channels revert to their respective resting (closed) conformations. Thus, a three-state kinetic scheme conceptually describes the changes in VGSC con-

formation that accounts for the changes in Na^+ (and K^+) conductance during depolarization and repolarization.

The commonly used local anesthetics are tertiary amines that exist in a dynamic equilibrium between a neutral lipid- soluble form and a hydrophilic, positively charged form, depending on pK_a and the pH of the aqueous milieu where the local anesthetic is administered. Both ionized and nonionized compounds with local anesthetic activity can inhibit VGSCs. Permanently neutral local anesthetics (e.g., the secondary amine benzocaine) freely permeate the lipid bilayer membrane and inhibit inward Na^+ conductance and impulse conduction, whether administered extracellularly or directly intracellularly, demonstrating that ionization is not absolutely required for local anesthetic activity. In contrast, quaternary ammonium derivatives of local anesthetics (QX-314 and QX-222), which are permanently charged and have very little membrane permeability, exhibit potent inhibition of Na^+ conductance and conduction block only when they are directly administered into the axoplasm [5]. Thus, tertiary amines must first permeate and traverse the lipid bilayer milieu in the neutral form, and having reached the axoplasm, become ionized to bind more avidly to the local anesthetic receptor within the VGSC.

In the presence of local anesthetics, VGSC activity is decreased by 30–50%, with low-frequency nerve stimulation, which is known as *tonic block*. While the neutral local anesthetic benzocaine exhibits little change in VGSC inhibition with an increased frequency of stimulation (depolarization), tertiary amines and permanently charged local anesthetic analogs exhibit increased VGSC inhibition when the axonal membrane is repetitively depolarized, known as *use-dependent (phasic) block* [6]. Increasing the frequency of stimulation increases the likelihood that VGSCs will exist in open and inactivated forms compared to the resting (closed) unstimulated state. Thus, the binding site for tertiary amine local anesthetics is thought to be located within the pore of the VGSC, and therefore not accessible when the channel is in the closed state. As a result, the terms *guarded receptor hypothesis* or *modulated receptor hypothesis* have been suggested. These theories indicate that local anesthetics bind preferentially to the VGSCs that are either open or inactivated, either because they are impeded from accessing the axoplasmic receptor site when the channel is closed ("guarded"), or because they may bind to the closed state of the channel with lower affinity (the receptor site is "modulated" by the channel conformation). More specifically, the open and inactivated conformations exhibit greater local anesthetic activity then do the closed, resting conformation. Thus, temporal changes in membrane potential influence both the VGSC conformation and affinity for local anesthetics. Local anesthetics, once bound to the channel, stabilize and prolong the duration of the inactivated state, thus inhibiting VGSC opening during further depolarization. The process of local anesthetic dissociation, which would allow the VGSC to return to its resting conformation, occurs at a much slower rate than the rapid voltage regulated return to the resting conformation that occurs during the physiological process of repolarization.

Local anesthetic interactions with G-protein-coupled receptor systems

GPCRs are integral cell-membrane proteins that work indirectly (through an intermediary) to activate a separate membrane-associated enzyme or ion channel. The intermediaries are heterotrimeric guanosine triphosphate (GTP) binding complexes called G proteins, which couple membrane receptors to intracellular signaling pathways.

Ca^{2+}-signaling GPCRs, which are GPCRs linked to release of Ca^{2+} from intracellular stores, have been identified as a target for local anesthetic activity [7]. More specifically, the inflammatory modulating effects of local anesthetics may result from interactions with GPCR mediated inflammatory signaling. Inhibition of GPCRs may occur at local anesthetic concentrations that are easily reached systemically during clinical use.

The mechanisms of action of local anesthetics on GPCR signaling have been elucidated predominantly via studies in heterologous expression systems, such as *Xenopus* oocytes, where it is assumed that the enzymes that couple the GPCR to the measured endpoint are the same as those in mammalian cells expressing that particularGPCR. When expressed in *Xenopus* oocytes, Ca^{2+}-signaling GPCRs activate one of several G proteins, which in turn activate phospholipase C (PLC). Activated PLC cleaves membrane phosphatidylinositol bisphosphate (PIP_2) into inositol trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 induces Ca^{2+} release via activation of a receptor channel on intracellular stores. The increase in Ca^{2+} can be measured and used as an index of GPCR activity. For almost all the local anesthetic sensitive GPCRs, the site of local anesthetic action can be localized to the G-protein–receptor interface. More specifically, G proteins linked to G_q α subunits have been identified as distinctively sensitive to local anesthetics, based on the known G-protein coupling of susceptible pathways [8]. This theory has been confirmed by studies where G_q was "knocked out" of a system with accompanying loss of local anesthetic sensitivity, while pathways not coupled to G_q remained unaffected.

Acute pain is often accompanied by inflammation, and certain inflammatory responses are exquisitely sensitive to local anesthetics via GPCRs. Studies on human polymorphonuclear leukocytes (PMNs) have helped to define the effects of local anesthetics on inflammation. PMNs play a crucial role in the inflammatory response, and since they do not express Na^+ channels, they are well suited to investigations on alternative sites of actions of

local anesthetics. Inparticular, the priming of PMNs, which is the process whereby the response of PMNs to a subsequent activating stimulus is potentiated, is often crucial for their rapid and vigorous response during inflammation. This priming has been shown to be a critical component of PMN-mediated tissue injury both in vitro and in vivo. It has been shown that priming is suppressed by local anesthetic concentrations commonly observed after intravenous or epidural administration, without interfering with the activation process of PMNs [9]. These findings provide a likely explanation why local anesthetics prevent overactive inflammatory responses without impairing host defenses or suppressing normal inflammation.

Physicochemical properties and relationships to activity and potency

The clinically useful local anesthetics consist of a lipophilic, substituted benzene ring linked to a hydrophilic amine group (tertiary or quaternary depending on pK_a and pH) through an intermediate chain consisting of either an ester or an amide linkage (Fig.1). The type of linkage separates the local anesthetics into two chemically distinct classes. Plasma cholinesterase enzymes hydrolyze the aminoesters, while aminoamides undergo enzymatic biotransformation in the liver. The clinically useful aminoamide local anesthetics can be further classified based on whether the hydrophilic amino end is a straight carbon chain (e.g., lidocaine) or the amino nitrogen is within a ring structure (pipecoloxylidide, e.g., bupivacaine). The clinical activity of local anesthetics is dependent on several important physicochemical properties [11], which determine the potency, duration of action, and tendency for differential nerve block (Table 2).

Lipid solubility

The aromatic ring is the primary determinant of the lipophilic nature (lipid solubility) of local anesthetics. Lipid solubility correlates with the tendency of the local anesthetic to associate with and penetrate through the axonal membrane lipid bilayer and into the axoplasm, and is largely determined by the degree of alkyl substitution on either the aromatic ring or the remaining structure [13]. For example, in the mepivacaine group (*N*-alkylpiperidine xylidide) of the amide local anesthetics, a change from a methyl to a butyl substitution on the tertiary amino group onverts mepivacaine to bupivacaine, which increases lipid solubility 26-fold. In contrast, a minor shortening of the 4-carbon butyl group of bupivacaine to a 3-carbon substitution (propyl) converts the compound to ropivacaine, which is approximately 4.5 times less lipid-soluble than bupivacaine (Fig. 1).

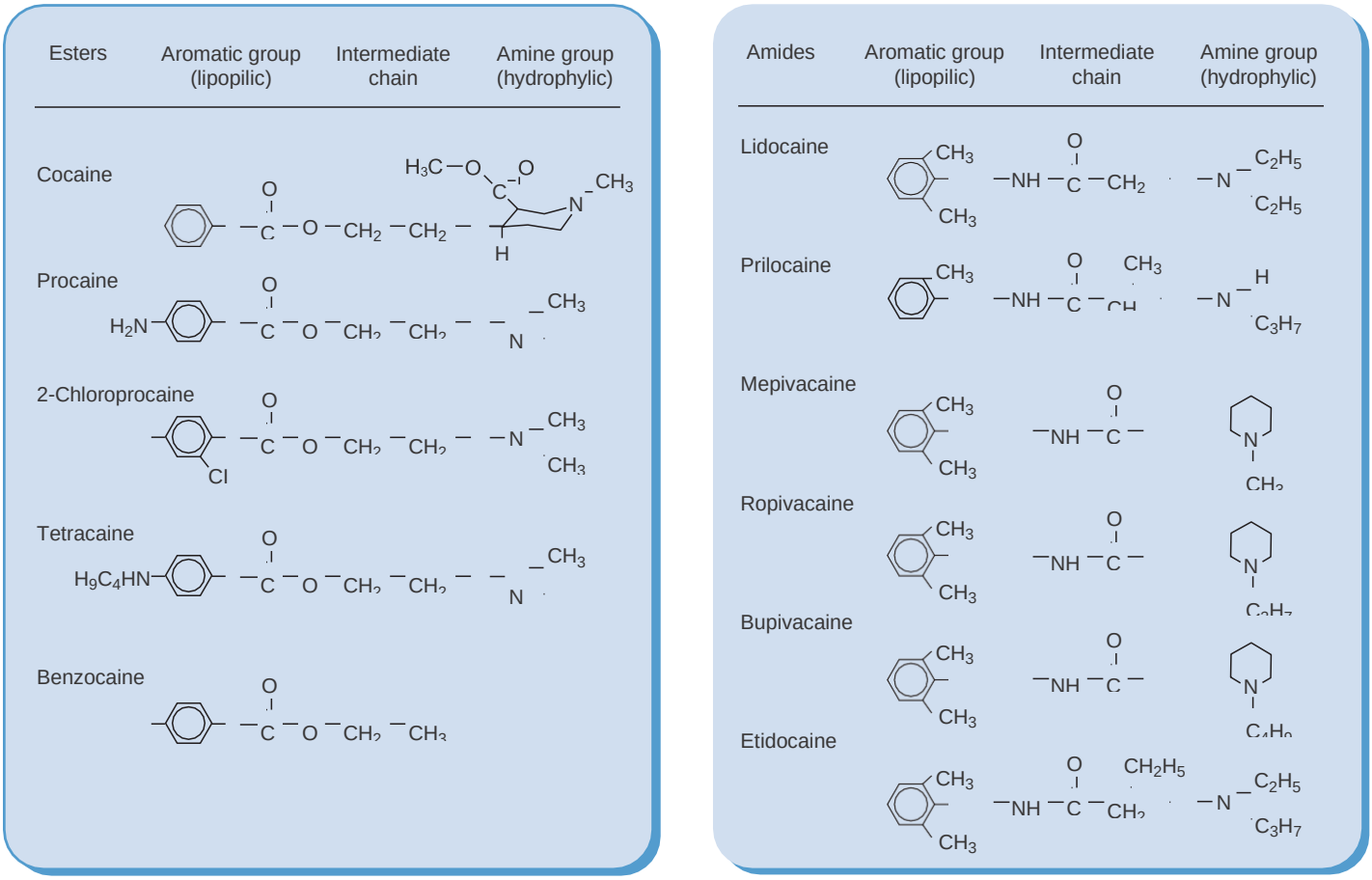

Figure 1: Local anesthetic structures. Clinically useful local anesthetics consist of an aromatic benzene ring linked to a hydrophilic amine group through an intermediate chain consisting of either (A) an ester or (B) an amide linkage. Benzocaine, a drug used primarily for topical anesthesia, is the only clinically useful local anesthetic lacking a tertiary amine group. Local

anesthetics connected through an ester linkage are metabolized by plasma cholinesterases. Local anesthetics connected through an amide linkage are metabolized in the liver by microsomal enzymes. Adapted from Butterworth [10].

Table 2: Physicochemical properties of clinically used local anesthetics

Local anesthetic	pK_a	% Ionized (at pH 7.4)	Partition coefficient (lipid solubility)	% Protein binding
Amides				
Bupivacaine	8.1	83	3420	95
Levobupivacaine	8.1	83	3420	> 97%
Etidocaine	7.7	66	7317	94
Lidocaine	7.9	76	366	64
Mepivacaine	7.6	61	130	77
Prilocaine	7.9	76	129	55
Ropivacaine	8.1	83	775	94
Esters				
Chloroprocaine	8.7	95	810	NA
Procaine	8.9	97	100	6
Tetracaine	8.5	93	5822	94

Source: Liu [12]. NA, not available.

Protein binding

Protein binding also influences the clinical activity of local anesthetics, as only the unbound form is free to exert pharmacological activity. In general, increasing molecular weight also correlates with an increased degree of protein binding to both plasma and tissue proteins. Although the VGSC is a protein structure, it does not appear that the degree of local anesthetic protein binding correlates with increased affinity to the protein structure of the VGSC. Studies have suggested that the binding and dissociation of local anesthetic molecules from the VGSC occurs in a matter of seconds, irrespective of the degree of protein binding [14].

Plasma protein binding more closely correlates with the degree of protein binding on the extracellular axonal membrane. It is likely that highly protein bound local anesthetics are removed from the nerve at a decreased rate, resulting in slower uptake and absorption, which accounts for the increased duration of action. Thus, increased protein binding correlates with increased lipid solubility, which leads to increased potency and duration of action of the local anesthetic as a result of increased local anesthetic content within nerves.

Within the plasma compartment, local anesthetics are bound primarily to albumin and α_1-acid glycoprotein (AAG). Local anesthetics exhibit a low-affinity and high-capacity association with albumin and a high-affinity but low capacity association with AAG. Although local anesthetics bind to AAG preferentially, binding to AAG is easily saturated with clinically relevant doses of local anesthetics [15]. Once AAG binding capacity is saturated, additional local anesthetic is bound by albumin. Because the binding capacity of albumin is very high, it can continue to bind local anesthetics at plasma concentrations that may exceed clinically desired levels. Despite the high-capacity binding of albumin, elevated plasma local anesthetic levels may increase the risk of systemic toxicity by increasing the percentage of the unbound active form. This is because the degree of protein binding is concentration dependent and, as the transition from AAG binding to albumin binding occurs, the degree of plasma protein binding consistently decreases.

Plasma protein binding of local anesthetics is also determined by plasma pH, such that the percentage of local anesthetic that is protein-bound decreases as the pH decreases. Thus, with acidosis (as occurs with significant seizure activity secondary to CNS toxicity), the percentage of unbound active local anesthetic increases, even though the total plasma con- centration may remain the same. Other clinically relevant factors also influence the degree of plasma protein binding. AAG concentrations are decreased in pregnancy and in the newborn. In contrast, AAG is increased in a variety of pathophysiological conditions such as surgery, trauma, and certain disease states (e.g., uremia), with a subsequent increase in the extent of local anesthetic binding [16].

Ionization

Local anesthetics in solution are weak bases that exist in equilibrium between the neutral lipid-soluble and the charged (protonated) hydrophilic form. The pK_a (dissociation constant) of a local anesthetic is the pH at which the two forms are present in equivalent amounts. The combination of the perineural and axoplasmic pH and the pK_a of a specific local anesthetic determine the percentage of each form. The primary site of action of local anesthetics appears to be on the intracellular side of the transmembrane VGSC, and the charged form appears to be the predominantly active form within the axoplasm [17]. Thus, pK_a generally correlates with speed of onset, because penetration by the neutral lipid-soluble form across the lipid bilayer of the axonal membrane is the primary mechanism by which local anesthetics gain access to the local anesthetic binding site (Fig. 2). Additionally, local anesthetic uptake occuring as aresult of lipophilic absorption will shift the effective pK_a downward, further favoring the neutral base form; this will have the effect of limiting diffusion of local anesthetic away from the site of administration.

The percentage of local anesthetic molecules existing in the neutral lipid-soluble form at the physiological pH of 7.4 is inversely proportional to the pK_a of the specific local anesthetic.

Thus, the lower the pK_a for a given local anesthetic within a specific local tissue pH, the higher the percentage of local anesthetic that exists in the lipid-soluble form, which hastens the penetration of axonal membrane and onset of action. Sodium bicarbonate may be added to local anesthetic solutions in an attempt to raise their pH, thereby increasing the percentage of the uncharged lipid-soluble form and theoretically improving the onset of the block. In contrast, local anesthetic solutions may be less effective when administered into inflamed tissues, which may be acidic and hyperemic. The acidic milieu will result in an increased percentage of the lipid- insoluble protonated form, and the increased tissue blood flow may increase systemic absorption, further impairing the clinical activity of the administered local anesthetic.

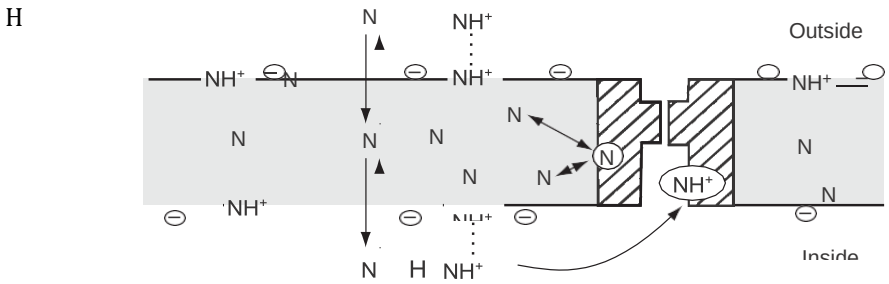

Figure 2: Diagram of bilayer lipid membrane of conductive tissue with Na$^+$ channel *(cross hatching)* spanning the membrane. Clinically useful local anesthetics exist in equilibrium between the lipid-soluble neutral (N) base and the charged (NH$^+$) hydrophilic form. The neutral base (N) preferentially partitions into the lipophilic membrane interior and easily passes into the membrane. The charged hydrophilic form (NH$^+$) binds to the Na$^+$ channel at the negatively charged membrane surface. The neutral form can cause membrane expansion and closure of the Na$^+$ channel. The charged form directly inhibits the Na$^+$ channel by binding with a local anesthetic receptor. Adapted from Strichartz [18].

Chirality

The majorityof clinically useful local anesthetics are formulated as racemic mixtures. Racemic compounds are 1:1 mixtures of two types of molecules (stereoisomers) bearing identical chemical composition and binding, but with a different three-dimensional spatial orientation around an asymmetric carbon atom Fig.3. Specifically, molecules with an asymmetric carbon exist in two forms that are mirror images of each other (i.e., they exhibit "handedness" or chirality), distinguished by how they rotate light according to the orientation of the structures in three dimensions (19).

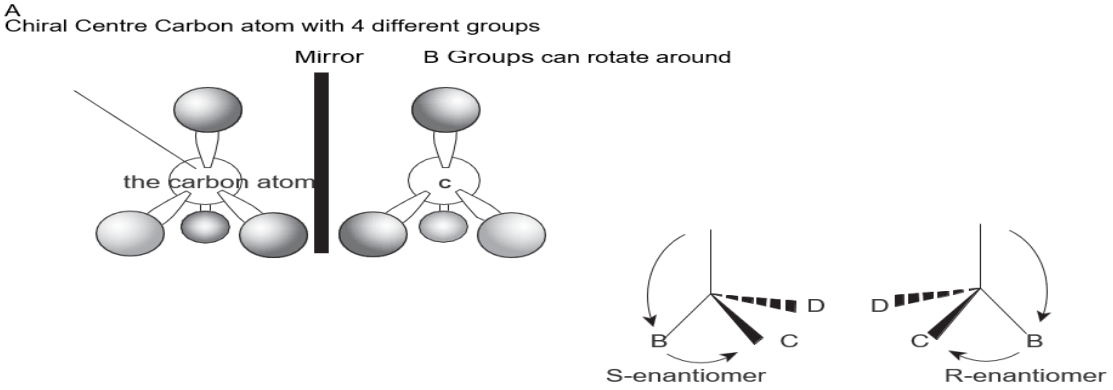

Figure 3: (A) Molecule with a chiral center and its enantiomers. (B) Three- dimensional projection of a pair of enantiomers that cannot be superimposed on each other. Bonds represented as solid lines are in plane, those drawn with dotted lines project away, and those represented by a wedge project toward the reader. Adapted from Burke and Henderson [19].

Local anesthetics exhibit a specific type of stereoisomerism termed *enantiomerism*, in which the pair of stereoisomers in three dimensional projection cannot be superimposed on each other. A notable exception is lidocaine, which is achiral. Although enantiomers of local anesthetics have identical physicochemical properties, they exhibit potentially different clinical pharmacodynamic (e.g., potency and potential for systemic toxicity) and pharmacokinetic profiles because of differences in their interactions with the biological receptor (VGSC).

Some clinically used local anesthetics are formulated as single stereoisomers. Examples of such clinically useful local anesthetics include ropivacaine (the S-enantiomer of the bupivacaine homolog, with a propyl alkyl group rather than a butyl group) and levobupivacaine (the S-enantiomer of bupivacaine). R-enantiomers of local anesthetics appear to have greater in-vitro potency for conduction block of both neuronal and cardiac Na^{+} channels, and thus would have the potential for greater therapeutic efficacy as well as the potential for systemic toxicity. In contrast, S-enantiomers (ropivacaine and levobupivacaine) have been shown to have equipotent clinical efficacy for neuronal conduction block, but a lower potential for systemic toxicity than either racemic mixtures or the R-enantiomer [20].

Additives to increase local anesthetic activity

Epinephrine is frequently added to local anesthetic solutions to cause vasoconstriction, and when used with larger volumes of local anesthetics (e.g., epidural and peripheral nerve blocks) it serves as a marker of intravascular injection [21]. The reported benefits of epinephrine include prolongation and increased intensity of local anesthetic block, as well as decreased systemic absorption of local anesthetic. The vasoconstrictive effects of epinephrine (and other α_1-agonists) augments local anesthetic activity via antagonism of the inherent vasodilating effects of local anesthetics [22]. Epinephrine decreases the rate of vascular absorption, thereby allowing more local anesthetics to reach the axonal membrane, which prolongs and increases the intraneural content of local anesthetics. Blood flow is decreased only briefly, and the block will persist long after the α_1-adrenergic effect on blood flow has resolved [23]. Additional analgesic effects from epinephrine may also occur through interaction with α_2-adrenoceptors in the spinal cord, which activate endogenous analgesic mechanisms via a direct pharmacodynamic mechanism [24]. The extent to which epinephrine prolongs the duration of local anesthetic block largely depends on the specific local anesthetic used and the site of administration. The most commonly used dose is 5 μg mL^{-1}, but doses as low as 1–2 μg mL^{-1} may be sufficient.The smallest effective dose should be utilized, as epinephrine in combination with local anesthetics may potentially have toxic effects on tissue, the cardiovascular system, peripheral nerves, and spinal cord [21].

Alkalinization

Alkalinization of local anesthetic solutions by the addition of sodium bicarbonate has been reported to speed the onset of conduction block. The pH of commercial local anesthetic solutions ranges from 3 to 7, and they are especially acidic if prepackaged with epinephrine. As the pK_a of commonly used local anesthetics ranges from 7.6 to 8.9 (Table 2), less than 3% of a commercially prepared local anesthetic exists in the lipid-soluble neutral form. Addition of sodium bicarbonate will increase the pH of the solution, which should increase the percentage of the lipid-soluble form and enhance the rate of diffusion across the nerve sheath and axonal membrane. However, local anesthetic solutions cannot be alkalinized beyond a pH of 6–8 before precipitation occurs [25], and these ranges of pH will only serve to increase the percentage of the neutral form to approximately 10%. There are conflicting data as to whether addition of sodium bicarbonate actually speedsthe onset of local anesthetic block; if so, it may only decrease the latency by 5 minutes. The differences may be related to the magnitude of the pH changes and the use of local anesthetic solutions prepackaged with epinephrine. One would expect that addition of sodium bicarbonate would have its greatest impact when added to local anesthetic solutions prepackaged with epinephrine, as these solutions have a lower pH compared to epinephrine-free (plain) solutions [26]. Additionally, an animal study demonstrated that alkalinization of lidocaine actually decreasedthe duration of peripheral nerve block if the solution did not contain epinephrine [27]. Thus, the value of alkalinization of local anesthetics may be questioned as a clinically useful tool to improve the onset of local anesthetic block.

Opioids

Opioids are commonly added to local anesthetic solutions for spinal and epidural anesthesia as a means to increase the density and duration of the local anesthetic block. The receptor site for opioids administered in the intrathecal or epidural space is within the gray matter of substantia gelatinosa located in the dorsal horn of the spinal cord. Opioids bind to presynaptic and postsynaptic receptor sites, which selectively blocks transmission of afferent nociceptive stimuli from Aδ and C fibers [28]. Presynaptic effects include release of spinal adenosine, which seems to be an important mediator specific for spinally mediated analgesia, as well as inhibition of Ca^{2+} influx and the subsequent release of glutamate and neuropeptides (such as substance P) from primary afferent terminals [29]. Postsynaptic effects include an increase in K^{+} conductance, hyperpolarizing ascending second-order projecting neurons without affecting somatosensory or motor evoked potentials [30].

Pharmacokinetics of local anesthetics

Plasma concentrations after administration of local anesthetics for neural blockade are determined by the rate of absorption from the site of injection, the rate of tissue distribution, and the rate of elimination of the specific local anesthetic drug. Patient specific factors such as age, cardiovascular and hepatic function, and degree of plasma protein binding influence the free plasma levels of local anesthetics, which ultimately determine the potential for systemic toxicity [31].

Systemic absorption

In general, local anesthetics with decreased systemic absorption will have a greater margin of safety in clinical use. The site of injection, the total dose and physicochemical properties of the specific local anesthetic, and addition of epinephrine determine the rate and extent of systemic absorption. The relative amounts of fat and tissue perfusion surrounding the site of administration will interact with the physicochemical properties of the local anesthetic to affect the rate of systemic uptake. In general, areas with greater tissue perfusion will have more rapid and complete uptake than those with more fat, regardless of type of local anesthetic. Thus, rates of absorption generally decrease in the following order: interpleural > intercostal > caudal > epidural > brachial plexus > sciatic/femoral > subcutaneous tissue (Table 3).

Table 3: Typical peak plasma levels after regional anesthesia with commonly used local anesthetics.

Local anesthetic	Technique	Dose (mg)	C_{max} (μg mL^{-1})	T_{max} (min)	Toxic plasma concentration (μg mL^{-1})
Bupivacaine	Brachial plexus	150	1.00	20	3
	Celiac plexus	100	1.50	17	
	Epidural	150	1.26	20	
	Intercostal	140	0.90	30	
	Lumbar sympathetic	52.5	0.49	24	
	Sciatic/femoral	400	1.89	15	
Lidocaine	Brachial plexus	400	4.00	25	5
	Epidural	400	4.27	20	
Local anesthetic	Technique	Dose (mg)	C_{max} (μg mL^{-1})	T_{max} (min)	Toxic plasma concentration (μg mL^{-1})
Mepivacaine	Brachial plexus	500	3.68	24	5
	Epidural	500	4.95	16	
	Intercostal	500	8.06	9	
	Sciatic/femoral	500	3.59	31	
Ropivacaine	Brachial plexus	190	1.30	53	4
	Epidural	150	1.07	40	
	Intercostal	140	1.10	21	
Levobupivacaine	Brachial plexus	150	0.96	43	
	Epidural	150	1.02	24	

Cmax: Peak Plasma Levels, **Tmax:** Time Until Cmax

The greater the total dose of local anesthetic injected, the greater the systemic absorption and peak blood levels (C_{max}). Within the clinical range of doses used for local anesthetics, this relationship is nearly linear and is relatively unaffected by anesthetic concentration [34] and speed of injection [35]. Physicochemical properties of local anesthetics will affect systemic absorption. In general, the more potent drugs with greater lipid solubility and protein binding will result in lower systemic absorption and C_{max}. Increased binding to neural and nonneural tissue probably explains this observation. Effects of epinephrine have been previously discussed. In brief, epinephrine can counteract the inherent vasodilating characteristics of most local anesthetics. The reduction in C_{max} with epinephrine is most effective for the less lipid- soluble, less potent, shorter acting drugs, because increased tissue binding rather than local blood flow may be a greater determinant of absorption for the long-acting drugs.

Distribution

After systemic absorption, local anesthetics are rapidly distributed throughout all body tissues, but the relative concentration in different tissues depends on organ perfusion, partition coefficient, and plasma protein binding. The end organs of main concern for systemic toxicity are the cardiovascular system (CVS) and central nervous system (CNS), because they are considered members of the “vessel rich group” and will have local anesthetic rapidly distributed to them. Despite the high blood perfusion, regional blood and tissue levels of local

anesthetics within these organs will not initially correlate with systemic blood levels, because of hysteresis [36]. Because regional and not systemic pharmacokinetics govern subsequent pharmacodynamic effects, systemic blood levels may not correlate with effects of local anesthetics on end organs [37]. Regional pharmacokinetics of local anesthetics for the heart and brain have not been fully delineated, and thus the volume of distribution at steady state (V_{dss}) is often used to describe local anesthetic distribution (Table 4). However, V_{dss} describes the extent of total-body distribution and may be inaccurate for specific organ systems. Whole body and regional pharmacokinetics for local anesthetics are also influenced by general anesthesia, which decreases whole body distribution and clearance and therefore significantly increases the plasma concentrations of local anesthetics [40].

Table 4: Pharmacokinetic parameters of clinically used local anesthetics

Local anesthetic	V_{dss} (L kg^{-1})	CL (L kg^{-1} h^{-1})	$t_{1/2}$ (hours)
Bupivacaine	1.02	0.41	3.5
Levobupivacaine	0.78	0.32	2.6
Chloroprocaine	0.50	2.96	0.11
Etidocaine	1.9	1.05	2.6
Lidocaine	1.3	0.85	1.6
Mepivacaine	1.2	0.67	1.9
Prilocaine	2.73	2.03	1.6
Procaine	0.93	5.62	0.14
Ropivacaine	0.84	0.63	1.9

V_{dss}, volume of distribution at steady state; CL, clearance; $t_{1/2}$, half-life.
Sources: Denson [38] and Burm *et al*. [39].

Elimination

Clearance of aminoesters is primarily dependent on hydrolysis of the ester bond by plasma cholinesterases. The rate of enzymatic degradation varies, with chloroprocaine being the most rapid, tetracaine being the slowest, and procaine being intermediate. Aminoamides are metabolized in the liver by the cytochrome P450 enzymes CYP1A2 and CYP3A4 via N- dealkylation, amide bond hydrolysis, and hydroxylation. The elimination of amide local anesthetics is highly dependent on hepatic function. Thus hepatic perfusion, extraction, enzyme function, as well as protein binding determine the rate of clearance of aminoamides. Impairment of hepatic function and decreases in hepatic perfusion (congestive heart failure) prolong the elimination of aminoamide local anesthetics.

Adverse effects and toxicity of local anesthetics

Allergic reactions

True immunologically mediated reactions to the local anesthetics are extremely rare [41]. Adverse reactions reported by patients administered local anesthetics may, in many cases, simply be a manifestation of systemic toxicity due either to elevated blood levels of local anesthetics, from absorption or from inadvertent intravascular injection, or to systemic effects of an additive, such as epinephrine [42]. While true allergic reactions to aminoamides are extremely rare, patients may have allergic reactions to aminoesters, and more specifically to the metabolite, para-aminobenzoic acid (PABA). Some local anesthetic solutions may be formulated with a preservative, methylparaben, which is structurally related to PABA and can cause a true allergic reaction.

Tissue toxicity

All clinically useful local anesthetics have the potential to produce direct toxicity to nerves if they achieve high enough intraneural concentrations. Laboratory studies have demonstrated that high concentrations of certain local anesthetics (lidocaine 5% and tetracaine 0.5%) applied directly to bare nerve fibers produce irreversible conduction block [43], while high concentrations of other local anesthetics result only in reversible conduction block without evidence of neurotoxic effects [44]. However, when local anesthetics are administered in clinical practice, the incidence of irreversible nerve injury is rare, because in the process of administration in the epidural space and peripheral perineural compartments they are sufficiently diluted due to vascular absorption and perineural compartment binding by fat and membrane proteins. Although most local anesthetics administered in clinical practice do not cause nerve damage, prolonged exposure, high doses, and/or high concentrations of local anesthetics at the spinal nerve roots may result in permanent neurological deficits.

In the late 1970s and early 1980s, there were reports of prolonged sensory and motor deficits (cauda equina syndrome [CES] and arachnoiditis) following the unintended intrathecal injection of large doses of chloroprocaine intended for epidural anesthesia [45,46]. The neurotoxic reactions in these cases were felt to be due to a combination of the low pH and sodium metabisulfite used in the formulation of chloroprocaine, in conjunction with inadvertent intrathecal administration of large

doses [47]. Chloroprocaine itself at high concentrations may also be directly neurotoxic, but these concentrations far exceed what is needed for local anesthetic blockade [48]. The reports of neurotoxicity have virtually disappeared with the introduction of preservative free chloroprocaine. Recent studies have demonstrated that small doses of preservative-free chloroprocaine intended for intrathecal anesthesia are effective and without neurotoxic effects [49,50]. Lidocaine has also been implicated as a cause of CES when used in high doses delivered via spinal microcatheters for continuous spinal anesthesia [51]. Subsequent investigations concluded that administration of inappropriately large doses of lidocaine (as a resultof repeated dosing) via the spinal microcatheters facilitated localized sacral pooling of high concentrations of the drug, thereby leading to high intraneural concentrations around the sacral roots and resultant neurotoxicity [52].

Subsequent to the reports of CES, intrathecal lidocaine has become associated with a condition known as transient neuro- logical syndrome (TNS) [53]. Symptoms of TNS manifest hours after resolution of spinal anesthetic, and include pain and paresthesia in the lower back, buttocks, and lower extremities, but without any sensory or motor deficits [54]. Although the discomfort may be moderate to severe, the syndrome is short-lived, typically resolving within 1 week. The exact mechanism of TNS is unknown; it has been reported after spinal anesthesia with most of the clinically useful local anesthetics, but is much more commonly associated with lidocaine spinal anesthesia [55].

Systemic toxicity

Methemoglobinemia

Benzocaine and a metabolite of prilocaine (o-toluidine) may cause clinically significant methemoglobinemia, a condition in which the ferrous form (Fe2þ) of hemoglobin is oxidized to the ferric form (Fe3þ). While in this oxidized state, hemoglobin cannot bind or transport oxygen. Normally, cytochrome b5, which is regenerated by the enzyme methemoglobin reductase, maintains iron in its reduced state, but has a limited reducing capacity in the presence of an increased amount of an external oxidizing compound, such as benzocaine [56,57]. Serious cases of methemoglobinemia present with central cyanosis that is refractory to oxygen therapy, which may be fatal if unrecognized. Diagnosis requires a high index of suspicion, which is confirmed by qualitative measurements of methemoglobinemia by co oximetry. Treatment consists of intravenous methylene blue (1–2 mg kg–1), which accelerates the reduction of methemoglobinemia via an alternative pathway for hemoglobin reduction.

Central nervous system toxicity

Local anesthetics readily cross the blood–brain barrier and produce a dose-dependent pattern of CNS symptoms. Signs of generalized CNS toxicity caused by local anesthetics are dependent on the plasma concentration of the particular drug (Table 5); elevated local anesthetic plasma concentrations can result from either systemic absorption or direct intravascular administration. Low plasma concentrations produce CNS depression, whereas higher plasma concentrations result in progressive CNS excitation that may lead to seizures [58]. As the plasma concentration of local anesthetics progressively increases, both inhibitory and facilitatory neurons are blocked, leading to generalized CNS depression. The incidence of seizures varies after different regional anesthetic techniques [59–61], as would be expected because of differences in the likelihood of unintentional intravascular injection or systemic absorption (Table 6).

Table 5: Dose-dependent systemic effects of lidocaine

Plasma concentration (μg mL^{-1})	Effect
1–5	Analgesia
5–10	Lightheadedness Numbness of tongue Tinnitus Muscular twitching
10–15	Seizures Unconsciousness
15–25	Coma Respiratory arrest
> 25	Cardiovascular depression

Table 6: Incidence of seizures after regional anesthesia in the United States and Europe

Anesthesia	Procedures *(n)*	Seizures *(n)*	Incidence of seizures (incidence /10 000)
Peripheral nerve blocks	72 756	37	5
Epidural caudal	77 871	18	2.3
Intravenous regional	11 229	3	3

Sources: Auroy *et al*. [62], Brown *et al*. [63], Auroy *et al*. [64].

The potential for systemic CNS toxicity approximately parallels the intrinsic anesthetic potency of the various local anesthetic drugs. In addition, decreased local anesthetic protein binding and clearance will increase potential CNS toxicity. A more rapid rate of intravenous administration of local anesthetic will also affect signs of CNS toxicity, because the accelerated rate of increase in plasma concentration will decrease the plasma concentration needed to induce seizures [65]. External factors can increase potential for CNS toxicity, such as acidosis and increased P_aCO_2, perhaps through increased cerebral perfusion or decreased protein binding of local anesthetic. There are also external factors that can decrease the potential for generalized CNS toxicity. For example, seizure thresholds of local anesthetics are increased by administration of barbiturates and benzodiazepines [66]. Epinephrine is frequently added to local anesthetic solutions to decrease the rate and extent of systemic absorption. The reduction in C_{max} should contribute to an increased margin of safety. However, the convulsive threshold for systemically administered local anesthetics with epinephrine is significantly decreased compared with that of plain solutions. The mechanism by which epinephrine increases systemic toxicity has not been fully elucidated and is likely to be multifactorial [67]. Epinephrine results in hypertension via peripheral vasoconstriction and a hyperdynamic circulation, which may augment systemic toxicity via increased cerebral perfusion and local anesthetic delivery to the CNS [68]. It has been demonstrated that epinephrine added to local anesthetic solution significantly increases the unbound plasma concentration of local anesthetics, resulting in increases in the extracellular concentration in the brain compared to administration of local anesthetics without epinephrine [69]. Thus, it appears that epinephrine may augment CNS toxicity by increasing the pharmacologically active free fraction available for transport across intracerebral neurons.

Cardiovascular toxicity

In general, significantly larger doses of local anesthetics are required to produce cardiovascular system (CVS) toxicity than CNS toxicity. Similar toCNS toxicity, the potential for CVStoxicity parallels the anesthetic potency of the drug. The morepotent, more lipid-soluble drugs (bupivacaine, etidocaine, and ropivacaine) appear to have an inherently greater cardiotoxicity than the less potent drugs. In addition, the more potent drugsappear to have a different sequence of CVS toxicity compared with the less potent drugs. For example, increasing doses of lidocaine lead to hypotension, bradycardia, and hypoxia, whereas bupivacaine often results in sudden CVS collapse caused by ventricular dysrhythmias that are resistant to resuscitation [70]. The more potent local anesthetics appear to possess greater potential for direct cardiac electrophysiological toxicity.A study examining lidocaine, bupivacaine, and ropivacaine in rats has demonstrated equivalent peak effects on myocardial contractility but much greater effects on electrophysiology (prolongation of QRS) from bupivacaine and ropivacaine thanfrom lidocaine [71]. Although all local anesthetics block the cardiac conduction system through a dose dependent block of $Na^þ$ channels, two features of bupivacaine's $Na^þ$-channel blocking abilities may enhance its cardiotoxicity. First, bupivacaine exhibits a much stronger binding affinity to resting and inactivated $Na^þ$ channels than lidocaine [72]. Second, local anesthetics bind to $Na^þ$ channels during systole and dissociate during diastole. Bupivacaine dissociates from $Na^þ$ channels during cardiac diastole much more slowly than lidocaine. Indeed, bupivacaine dissociates so slowly that the duration of diastole at physiologic heart rates (60–180 beats per minute) does not allow enough time for complete recovery of $Na^þ$ channels and bupivacaine conduction block accumulates (Fig. 4). In contrast, lidocaine fully dissociates from $Na^þ$ channels during diastole and little accumulation of conduction block occurs [73]. Thus, enhanced electrophysiological effects of more potent local anesthetics on the cardiac conduction system may explain their increased potential to produce sudden CVS collapse through cardiac dysrhythmias.

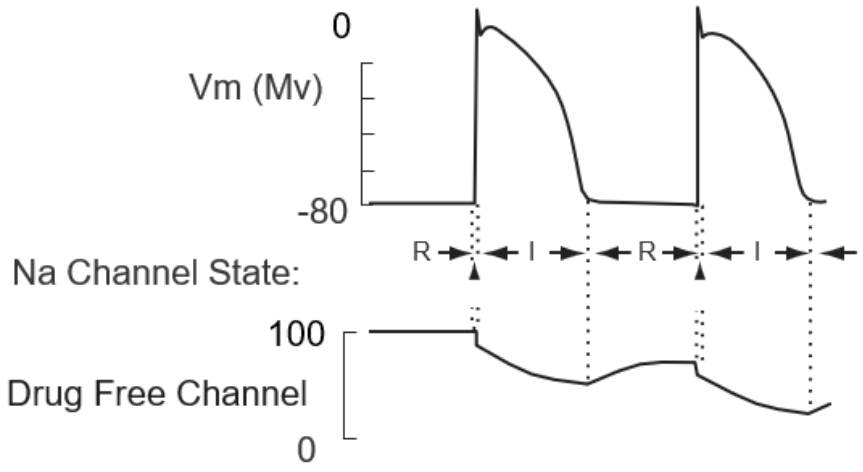

Figure 4: The relationship between cardiac action potential (top), sodium channel state (middle), and sodium channel block by bupivacaine (bottom). Sodium channels are predominantly in the resting (R) form during diastole, open (O) transiently during the upstroke of the action potential, and are in the inactive (I) form during the plateau of the action potential. Block of sodium channels by bupivacaine accumulates during the action potential (systole) with recovery occurring during

diastole. Recovery of sodium channels occurs by dissociation of bupivacaine and is time-dependent. Recovery during each diastolic interval is incomplete and results in accumulation of sodium channel block with successive heart beats. Adapted from Clarkson and Hondeghem [73].

CNS-mediated mechanisms may also be involved in the increased cardiotoxicity of bupivacaine. The nucleus tractus solitarius in the medulla is an important region for autonomic control of the CVS [74]. Neural activities within the nucleus tractus solitarius of rats are markedly diminished by intravenous doses of bupivacaine immediately before the development of hypotension. Furthermore, direct intracerebral injection of bupivacaine can induce sudden dysrhythmias and cardiovascular collapse [75]. Peripheral effects of bupivacaineon the autonomic and vasomotor systems may also augmentits cardiovascular toxicity. Bupivacaine possesses potent peripheral inhibitory effects on sympathetic reflexes [76] and also has potent direct vasodilating properties that may exacerbate cardiovascular collapse [77]. The multitude of different cardiacand neural mechanisms of cardiotoxicity may in part explain the reported difficulties of resuscitation after cardiovascular collapse from bupivacaine. Once cardiovascular collapse occurs, maintenance of respiration and myocardial perfusion are vital, because hypercapnia, hypoxia, acidosis, hypothermia, hyperkalemia, hyponatremia, and myocardial ischemia will all further sensitize the heart to bupivacaine cardiotoxicity [78].

New and emerging concepts

Over three decades ago, an editorial by Albright reported a series of cases of fatal CVS toxicity associated with use of the long-acting lipophilic local anesthetics bupivacaine and etidocaine, in which there was an alarming lack of response to standard resuscitative measures in otherwise healthy patients [79]. In this editorial, Albright highlighted that the potency of bupivacaine and etidocaine correlated with their propensity to cause severe CVS toxicity, often manifested by malignant ventricular dysrhythmias, progressing to cardiovascular collapse. The treatment for severe local anesthetic induced CVS with bupivacaine has largely been supportive, consisting of oxygenation and ventilation with positive pressure ventilation, in conjunction with standard advanced cardiac life support measures, including hemodynamic support with either epinephrine or vasopressin, pharmacological therapy with amiodarone, and cardioversion [58]. Inspite of these aggressive efforts, bupivacaine induced CVS toxicity may remain refractory, and cardiopulmonary bypass should be considered [80].

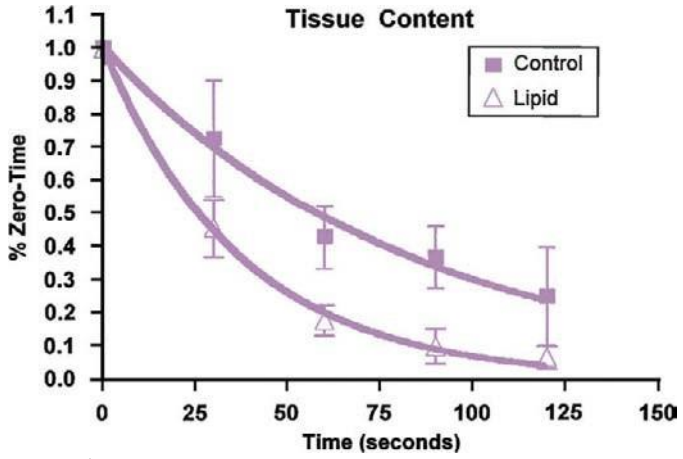

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Figure 5: Cardiac bupivacaine content. The trends for myocardial bupivacaine content are shown during 2 minutes after a 30-second infusion of bupivacaine 500 µmol L–1 for control and lipid-treated hearts. Values are normalized to zero time, and error bars indicate standard deviation (n 5 for both groups). Regression curves were fitted by single exponential decay functions with time constants 83 seconds (R2 0.9861) and 37 seconds (R2 0.9978) for control group and lipid groups respectively. Reproduced with permission from Weinberg et al. [83].

During a series of experiments studying the metabolic effects of bupivacaine, a group of investigators made the chance observation that pretreating rats with lipid soybeanoil emulsion resulted in marked resistance to the cardiac effects of bupivacaine infusion. In a series of experiments with progressively larger animal models, lipid emulsion therapy (consisting of a bolus followed by an infusion) was administered before [81] or after [82] bupivacaine induced cardiac arrest was established, and resulted in rapid hemodynamic recovery and uniform rescue from cardiac arrest compared to controls not given lipid emulsion. The mechanisms proposed for lipid emulsion's remarkable success included a "lipid sink" mechanism, where bupivacaine is removed from affected tissues (myocardium) by partitioning into a plasma lipid compartment created by the lipid. This hypothesis has been supported by a study clearly demonstrating that lipid emulsion not only accelerates recovery from bupivacaine toxicity, but also accelerates the removal of bupivacaine in an isolated rat heart model (Fig. 5) [83]. A complementary mechanism for the effectiveness of lipid emulsion is that it directly reverses bupivacaine-induced contractile dysfunction by providing an alternative source of intracellular fat content for myocardial metabolism, in the absence of normal fatty acid oxidative phosphorylation [84]. Subsequent to these animal

studies, the first case of lipid emulsion in the resuscitation of severe bupivacaine- induced CVS toxicity was reported in 2006 [85]. Since then, numerous other case reports have added to the clinical evidence of the remarkable efficacy of lipid emulsion in the treatment of severe local-anesthetic-induced CVS toxicity [86–88]. The current recommended dose is 1.5 mL kg^{-1} 20% Intralipid administered as bolus, followed by a continuous infusion of 0.25 mL kg^{-1} min^{-1} continued for an hour after resumption of sinus rhythm [89]. Future areas of research include additional studies on its mechanisms of actions, as well as optimization of the treatment regimen with regards to efficacy and safety.

Action potentials are the signals through which information is transmitted between electrically excitable cells of the central and peripheral nervous systems. Local anesthetics inhibit action potentials, thus interrupting afferent (sensory) signaling from various parts of the body to the brain. Local anesthetics are most often administered in close proximity to nerves within the peripheral and central nervous systems. Multiple layers protect the peripheral nerve, thus presenting a significant barrier to local anesthetics reaching their intended site of action within the axonal cell membranes.

The traditional mechanism of action of local anesthetics is via blockade of axonal action potential generation or propagation by prevention of the voltage-gated Na^{+} channel (VGSC) conductances that mediate these action potentials. Addition ally, local anesthetics interact with Ca^{2+} signaling and with G-protein coupled receptors (GPCRs), which may mediate their anti-inflammatory actions.

The clinical activity of local anesthetics is dependent on several important physicochemical properties, which determine the potency, duration of action, and tendency for differential nerve block:

- The aromatic ring is the primary determinant of the lipid solubility of local anesthetics, and, in turn, lipid solubility is the primary determinant of local anesthetic potency and duration of action.
- Protein binding also influences the clinical activity of local anesthetics, as only the unbound form is free to exert pharmacological activity. In general, increasing molecular weight correlates with increased protein binding to both plasma and tissue proteins.
- The site of action of local anesthetics is on the intracellular surface of the VGSC. Local anesthetics must therefore penetrate the cell to gain access to their site of action. Only the uncharged form of the drug can penetrate the membrane. The lower the pK_a of a given local anesthetic, the greater the proportion of the drug that is unprotonated and uncharged at physiological pH. Local anesthetics with lower pK_a thus have faster onset of action.
- The majority of clinically useful local anesthetics are formulated as racemic mixtures of two enantiomers (mirror image sterioisomers) that differ in local anesthetic potency. Several local anesthetics (ropivacaine and levobupivacaine) are marketed and administered as a single S-enantiomer. Use of a single enantiomer is thought to reduce toxicity and side effects.

Additives to increase local anesthetic activity include:

Epinephrine – Epinephrine decreases the rate of vascular absorption, thereby allowing more local anesthetics to reach the axonal membrane, which prolongs and increases the intraneural content of local anesthetics.

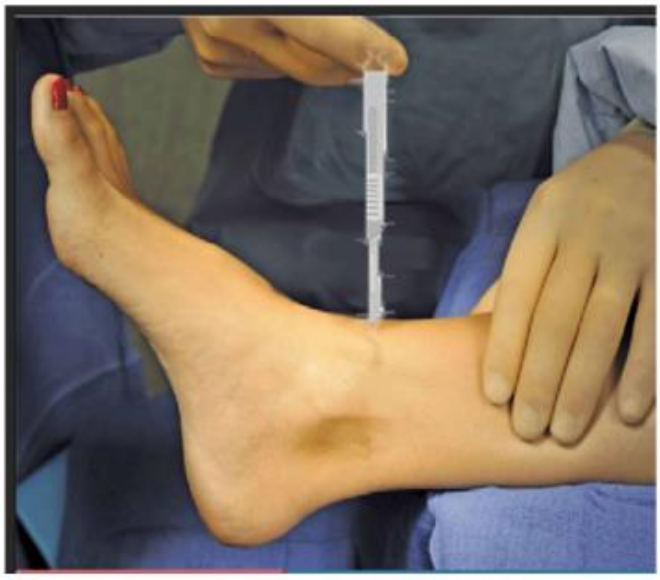
Alkalinization – Alkalinization of local anesthetic solutions by the addition of sodium bicarbonate has been reported to speed the onset of conduction block, but its clinical value is questionable.

Opioids – Opioids are commonly added to local anesthetic solutions for spinal and epidural anesthesia as a means of increasing the density and duration of the local anesthetic block. Opioids bind to presynaptic and post- synaptic opioid receptor sites, which selectively blocks transmission of afferent nociceptive stimuli.

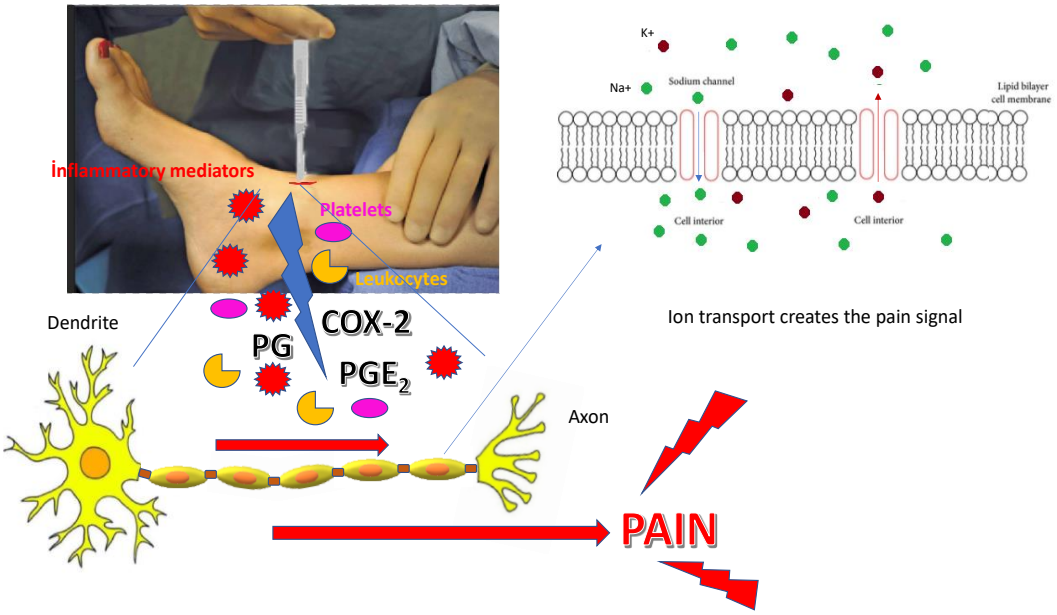
Plasma concentrations after administration of local anesthetics for neural blockade are determined by the rate of absorption from the site of injection, the rate of tissue distribution, and the rate of elimination of the specific local anesthetic. Local anesthetics with decreased systemic absorption will have a greater margin of safety in clinical use. The greater the total dose of local anesthetic injected, the greater the systemic absorption and peak blood levels (C_{max}); drugs with greater lipid solubility and protein binding will result in lower systemic absorption and C_{max}. After systemic absorption, local anesthetics are rapidly distributed throughout all body tissues, but the relative concentration in different tissues depends on organ perfusion, partition coefficient, and plasma protein binding. Elimination of aminoesters is primarily dependent on hydrolysis of the ester bond by plasma cholinesterase. Aminoamides are metabolized in the liver by the cytochrome P450 enzymes CYP1A2 and CYP3A4.

The major adverse reactions to local anesthetics are allergic reactions, methemoglobinemia, cardiovascular toxicity, and central nervous system toxicity. Infusion of lipid emulsions has been shown to be highly efficacious in treating the cardiovascular toxicity of local anesthetics.

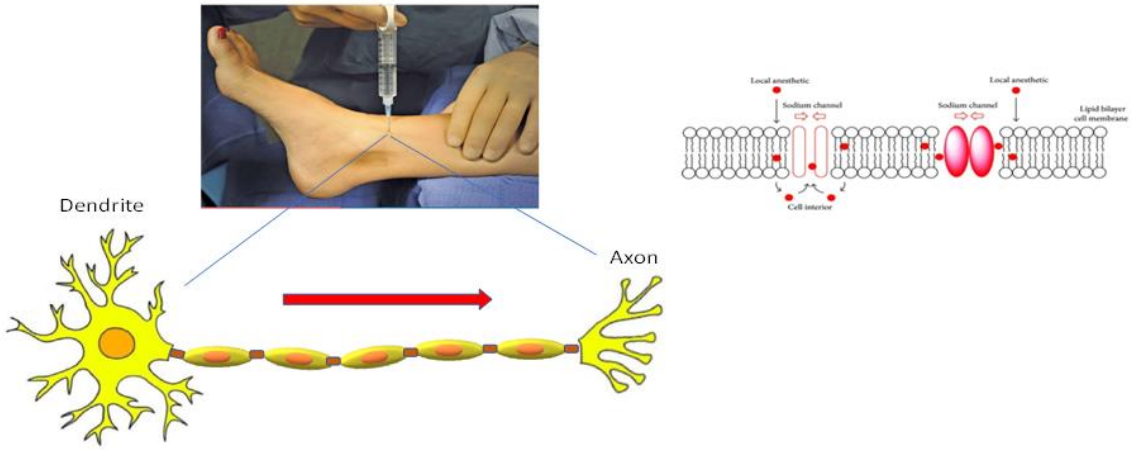
How Does Local Anesthesia Prevent Pain?
Here Is Example Explanation:



Photography and Drawing I: Image of a patient undergoing surgery (90)

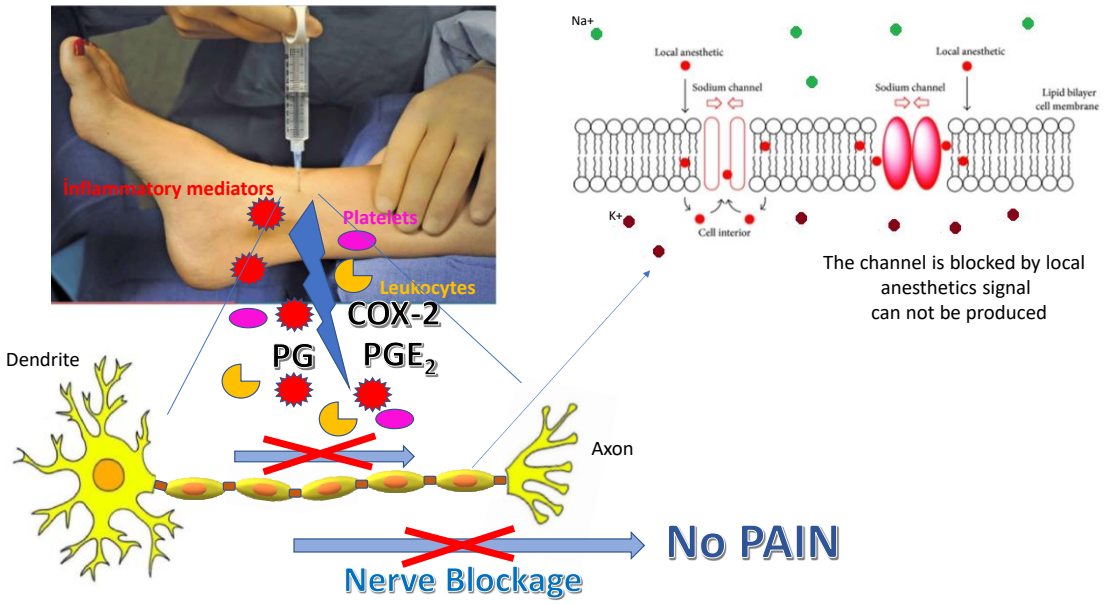


Photography and Drawing II: The mechanism of pain formation if the procedure is performed without applying local anesthesia. İnflammatory mediators, prostaglandins, ion transport along nerve conduction and severe PAIN. Membrane potential created by Na and K ions plays a role in nerve conduction. (91)

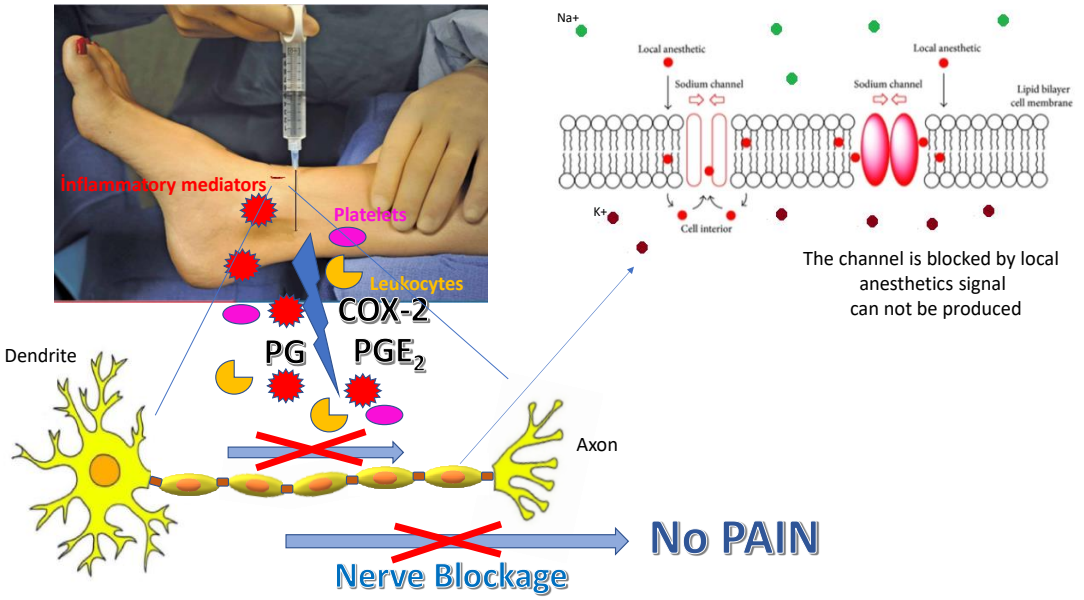


Photography and Drawing III: The process that occurs with application of local anesthetic before the surgical procedure.

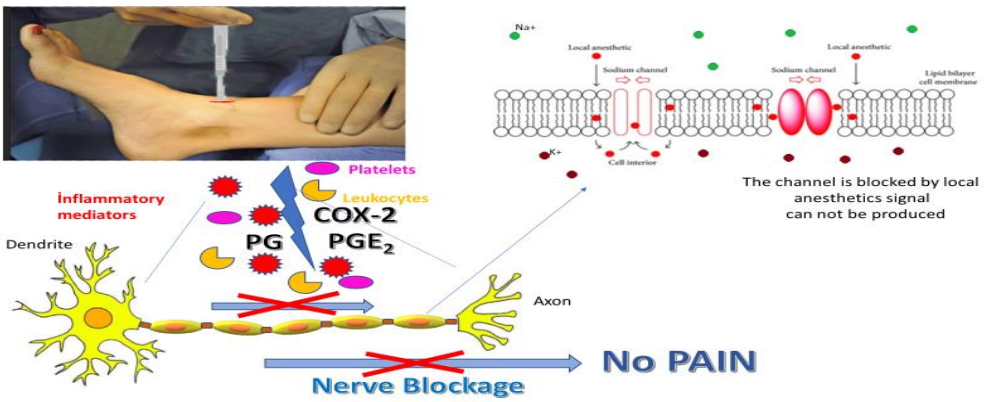
In this theory, it is thought that local anesthetics affect some specific receptors in Na channels and close these channels. Two types of receptors, one on the inner surface and one on the outer surface, are shown in Na channels (92).



Photography and Drawing IV: The changes in the ion channels of the local anesthetic effect made without pain with the surgical incision. Elimination of pain. (93)



Photography and Drawing V: The changes in the ion channels of the local anesthetic effect after the surgical incision is made and pain occurs. Elimination of pain. (94)



Photography and Drawing VI: And painless surgical procedure. (95)

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