Chapter

Local Anesthetics

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Abstract

The fascinating history of local anesthetics (LAs) began in South America with the herbal and traditional use of cocaine leaves by the indigenous peoples of Peru and Bolivia, the sacred plant of the Incas *Erythroxylum coca*. The use for anesthetic purposes dates back to 1884. Since then, the evolution of LAs has been closely related to research motivated by its efficacy and safety versus toxicity. According to their chemical structure, these drugs are classified into two main groups: esters and amino amides; however, there are three LAs with different characteristics: articaine, sameridine, and centbucridine. The pharmacological and toxic mode of action is primarily in the voltage-dependent sodium channels located in the cell membrane, which clinically produces analgesia, anesthesia, seizures, arrhythmias, and cardiac arrest. The quality of anesthesia and analgesia depends on the type of LA, dose, and application technique, while the deleterious effects are secondary to its plasma concentration. Nonanesthetic properties of LAs such as their antimicrobial, antineoplastic, antiarrhythmics, antitussive, and antiasthmatics effects have been described and are briefly reviewed.

Keywords: local anesthetics, pharmacology, toxicity

1. Introduction

Local anesthetics (LAs) are drugs commonly used in medicine and especially in anesthesiology, which when administered in the vicinity of peripheral neural tissue produce changes in the conformation of voltage-dependent sodium channels that depolarize the neural tissue and produce analgesia, anesthesia, and sympathetic and motor block in the dermatomes of the affected nerves without altering consciousness. This inhibitory phenomenon is reversible and transitory and is known as regional anesthesia and is classified into local, peripheral nerves, nervous plexuses, peridural, subarachnoid, and intravenous anesthesia.

LAs are safe and effective drugs, although when wrongly managed, they can reach high plasma concentrations and produce systemic toxicity (LAST) that manifests primarily in the central nervous system (CNS) and cardiovascular system (CVS), causing side effects that can occasionally lead to death. Local neuro toxicity has also been described when injected in the vicinity of the peripheral nervous system or at subarachnoid or epidural space. Myotoxic effects have also been described.

The main clinical use of LAs is to achieve pain insensitivity, although they have other pharmacological uses such as antiarrhythmic, anti-asthmatic, anti-inflammatory, antithrombotic, bacteriostatic, and bactericidal effects that have been demonstrated, as well as antitumoral agent enhancer activity [1–3]. LAs are grouped into two categories: those of the ester type and those of the amino-amide

group. They are the only drugs used in regional anesthesia, although it has been described that other drugs with different molecular structure such as amitriptyline, meperidine, eugenols, beta-adrenergic antagonists, alpha$_2$ agonists, spasmolytics, anticonvulsants, and antihistamines have local anesthetic effects [4–6]. There are three LAs that due to their chemical structure differ from the classic LAs: articaine, sameridine, and centbucridine. Articaine is classified into the amide group, it is fat soluble and short acting and has intermediate potency, with rapid metabolism due to an ester group in its structure. Sameridine, on the other hand, has mixed effects as an opioid agonist and LA properties under investigation for intrathecal use [7, 8]. Centbucridine is a nonester, nonamide drug still under clinical investigation [9].

In this introductory chapter, the most important properties of LAs are detailed, emphasizing their pharmacological classification, pharmacokinetic profile, action mechanisms, side effects, and some relevant clinical aspects, as well as their nonanesthetic uses.

2. Brief history of the discovery and evolution of LAs

In the Andean Mountains, centuries ago, the Incas began using cocaine leaves which they chewed or ingested in the form of potions that provided them with plenty of energy to carry out their religious rituals. In addition, as a powerful stimulant, the coca leaf was chewed to mitigate the effects derived from altitude, hunger or fatigue and as a medicine for gastrointestinal discomfort, colds, or bruises. This sacred plant of the Incas, *Erythroxylum coca*, caught the attention of Europeans who took it to the old continent at the end of the 16th century. It was until 1859 when Paulo Mantegazza, an Italian physiologist, wrote *Sulle virtu igieniche e Medicinale della Coca* (On the hygienic and medicinal properties of coca and on nervine nourishment in general) where he pointed out its healing properties. The German chemist Albert Niemann isolated the active substance from these leaves and called it cocaine, noting its power to anesthetize the tongue. In 1884, Sigmund Freud wrote his famous monograph entitled *Ueber coca.* Like some of his contemporaries, Freud acknowledged that cocaine had local anesthetic effects when applied to the mucous membranes, but it was Karl Köller who used it for the first time for anesthetic purposes when applied in various mucous membranes and in the conjunctiva for surgical purposes. It is Köller to whom it is attributed the beginning of local anesthesia [10–12].

The knowledge of the toxic and additive effects of cocaine became public quickly; it went from being the LA in vogue to a potent CNS stimulant that until today is a social stigma. This fired the investigation toward new LAs, and safer drugs were found. Benzocaine was synthesized in 1890, and in 1904, Alfred Einhorn introduced procaine by degrading cocaine, which was later marketed as novocaine® and was the most widely used LA in the world. Tetracaine was synthesized in 1928 and introduced into clinical anesthesia in 1932. In 1943 Löfgren discovered lidocaine that was introduced for clinical use in 1947 and is currently the most used LA. Mepivacaine appeared in 1956, and in 1963, the clinical use of bupivacaine was introduced, while etidocaine began to be used in 1972. Other LAs appeared during the following years but were withdrawn from the market due to their toxic effects. In 1970, Albrigth [13] mentioned some deaths attributed to bupivacaine and etidocaine. His editorial was enough to start basic and clinical research in search of new drugs with a better safety profile. The result was the introduction of ropivacaine in 1997 and levobupivacaine in 1999, both levoisomeric drugs. It is noteworthy that these two LAs had been discovered in 1957 and 1972, respectively (**Table 1**).

Local anesthetics	Year of synthesis	Introduction in clinic
Cocaine	1860	1884
Procaine	1904	1905
Dibucaine	1925	1930
Tetracaine	1928	1932
Lidocaine	1943	1947
Chloroprocaine	1950	1952
Mepivacaine	1956	1957
Prilocaine	1959	1960
Bupivacaine	1957	1963
Etidocaine	1971	1972
Ropivacaine	1957	1997
Levobupivacaine	1972	1999

Table 1.
Chronological appearance of local anesthetics.

The levoisomeric LAs did not replace other LAs but are complementary to the therapeutic armamentarium in regional anesthesia. Both ropivacaine and levobupivacaine have been conquering a special place in regional anesthesia techniques, but their toxicity is still superior to procaine, chloroprocaine, and lidocaine. While these LAs are not comparable in potency and duration, they still have a place in anesthesiology, with the exception of intrathecal lidocaine. The history of these drugs will continue to be written as new results on therapeutic effectiveness and toxicity are obtained.

3. Basics data

It is necessary to know some elementary aspects of the structure and function of the cell membrane, as well as to understand the role of voltage-dependent sodium channels, which are protein structures that are located in the cell membrane and play a paramount role in cellular electrical activity and impulse transmission.

3.1 Cellular membrane

The cell membrane is a barrier of lipids and proteins, which forms the outer surface of eukaryotic cells. The lipid part of the membrane is formed by a bilayer with a thickness of 60–100 Å, which gives it structure and constitutes a barrier that prevents the passage of water-soluble substances. It has three important types of lipids: phospholipids, glycolipids and cholesterol. The membrane proteins are suspended individually or in groups within the lipid structure and shape the various channels. The selectivity of transmembrane protein channels allows the cell to control the entry and exit of substances, as well as transport between cell compartments. Membrane proteins not only facilitate selective transport, but in addition, they are able to carry out active transport against the concentration gradient with special pumps, such as the sodium-potassium pump. Other functions of the membrane, such as the recognition and binding of certain substances on the cell surface, are also determined by the protein part of the membrane. These proteins are called cell receptors.

Cellular receptors are connected to internal systems that only act when certain substances bind to the membrane surface. Many of the cell controls act through this mechanism. Some metabolic pathways do not take action unless the "signal" molecule—for example—a hormone, has reached the cell surface. Glycoproteins are located in the membrane that identify other cells as members of an individual or as strangers. The interactions between the cells that make up a tissue are based on membrane proteins. In this manner, the structure of the membranes depends on the lipids, while the functions depend on the proteins.

3.2 Physiology of nerve transmission

The resting cell membrane maintains a voltage difference of 40–90 mV between the inner and outer layers, the inside being negative and the outside positive. This is the so-called resting potential, which is maintained by an active mechanism of the Na/K pump. The polarized membrane does not allow the passage of sodium ions ($Na^{+)}$ through the voltage-dependent sodium channels that are in resting state. When an electrical stimulus arrives, the membrane depolarization begins by activating the sodium channels that open to give way to the Na^+, which enter the intracellular medium, transforming the negativity of the transmembrane potential. This initiates a cycle of changes of sodium channels in four functional stages: resting, activated, inactivated, and deactivated. In the resting state, the outer gate of the sodium channel is closed, and the internal gate or closing gate is open. When a stimulus reaches the membrane, the sodium channel is activated by opening the external gate and letting Na^+ pass. When the membrane potential rises to +20 mV, the closure of the internal gate is triggered, and it enters an inactive state. The channel is deactivated when the membrane potential reaches −60 mV. When the passage of Na^+ ceases through the pore of the sodium channel, the potassium channel increases its permeability, allowing this ion to pass inside the cell due to differences in concentration (concentration gradient). Then the initial phase is restored; the Na-K pump mobilizes Na^+ outside and K^+ inside the cell. Sodium channels pass from the inactive-deactivated state to the initial resting state. All these movements of Na^+ and K^+ are manifested in changes in the transmembrane electrical potential, generating the action potential that is propagated along the nerve fiber (**Figure 1**) [14]. Because there is a potential difference across the cell membrane, the membrane is said to be polarized. If the membrane potential becomes more positive than it is at the resting potential, the membrane is said to be depolarized. This whole process lasts 1 millisecond; 30% is consumed by the depolarization phase. According to the electrical instant, the sodium channels dependent on voltage exist in four stages; resting (−90 mV), activated (−60 mV), inactivated (+20 mV) and deactivated (−60 mV).

3.3 Voltage-dependent sodium channels

Hodgkin and Huxley proposed that cell membranes contained channels that facilitated ionic passage through them, which was confirmed when ionic currents that selectively flow through these transmembrane pores were directly measured. In 1972, Singer and Nicolson [15–17] proposed the ¨Fluid Mosaic Model¨ in the structure of the cell membranes were they described the cell membrane as a two-dimensional liquid that restricts the lateral diffusion of membrane components and includes the integral proteins inserted in the lipid bilayer, some of which completely cross it and others cross it partially. Of these membrane proteins, three primary groups stand out: the channels, pumps, and receptors that constitute the transport system through cell membranes and regulate the movements of small molecules and ions that cannot pass through the lipid bilayer.

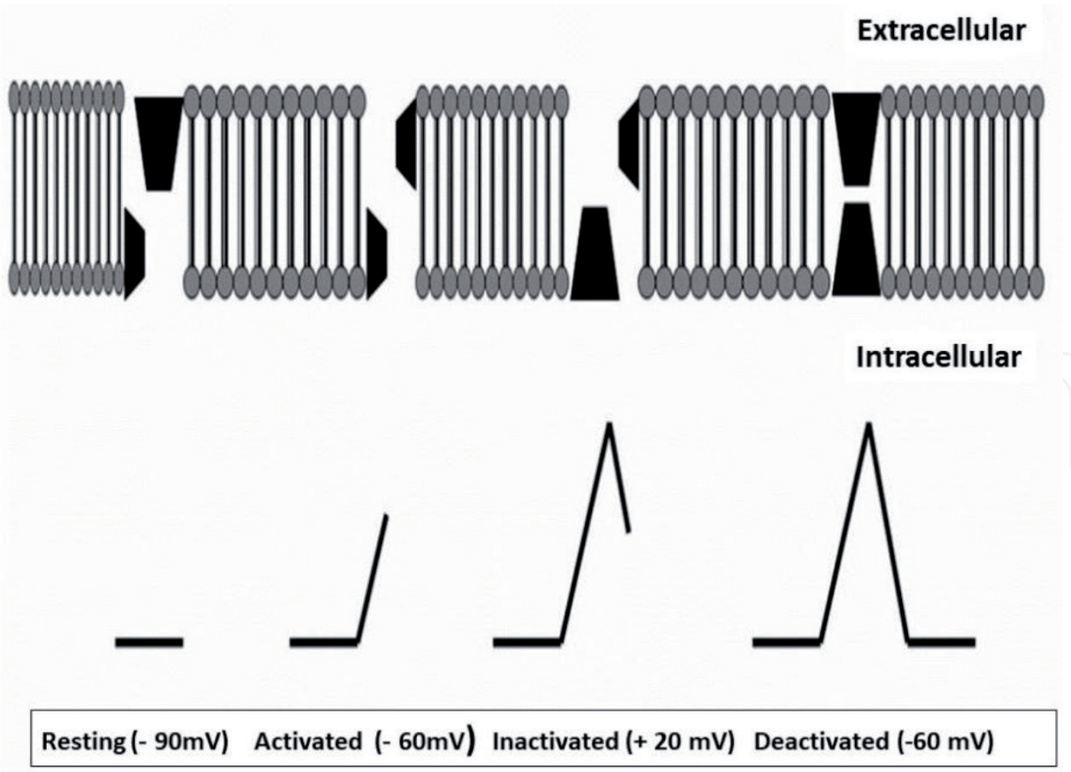


Figure 1.
Representation of the four structural phases of sodium channels and their relationship with the action potential. Modified from Columb MO, MacLennan K. Local anesthetics agents. Anaesth Intensive Care Med 2007; 8: 159–162 [14].

Sodium channels are protein structures that are integrated into the lipid bilayer of the cell membrane and are responsible for orchestrating the electrical signals that are transmitted by certain tissues, such as nerves and the heart's electrical conduction system. They are tubular-shaped components that resemble pores filled with water and are distributed through the whole cell membrane, primarily at the beginning of axons and in Ranvier nodes. This ion channels are divided into three types; those regulated by voltage, those regulated by extracellular ligand and those regulated by intracellular ligands, although other authors classify them into only two groups; those regulated by voltage and those operated by receptors [18–20]. The family of voltage-regulated sodium channels is composed of nine members that have been described in mammals and a tenth component related to a protein. All of them are members of a super family of ion channels that also includes potassium and calcium channels. Its nomenclature is complex and the chemical symbol of sodium Na^+ is used first, followed by V indicating voltage regulated (Na^+ V). The next number indicates the subfamily gene (Na^+ V1), and the next number identifies the specific isoform of the channel, for example Na^+ V1.1. This last number was assigned in the chronological order in which the genes were discovered. There are variants that come together or splice in each family member, which are told apart from each other by a lowercase letter, for example Na^+ V1.1. a. [18, 19].

The sodium channels are formed by an alpha subunit, a simple polypeptide with a relative molecular mass of ~260,000 and are responsible for the selectivity and gate voltage. Some sodium channels have beta 1 and 2 subunits. These sodium ionophores are made up of four homologous domains; each of these four domains contains six transmembrane segments known as alpha-helices. This causes each sodium channel to cross the cell membrane 24 times. The center of this structure is the channel pore through which the Na^+ passes into the interior of the cell and also the LAs in their hydrophilic form on their way to be fixed in the internal pore of the

sodium channel, where the voltage sensor is located. This voltage sensor is located in the fourth segment of each domain, where the LAs are fixed in the sixth segment of Domains 3 and 4. The voltage sensor has a very high positive charge, and these four domains are connected to each other by segments or hydrophilic bridges formed by amino acids that are located on the extracellular side of the membrane. The bridge that joins segments 5 and 6 of each domain is known as a pore handle and covers the pore of the channel to allow only the passage of Na^+. This channel structure is responsible for selectivity and is vulnerable to certain toxins that can inactivate the sodium channel, although another description mentions that the selectivity filter is given by a narrowing of the ionic pore located below its gate [19].

The gate of the ionic pore is the initial portion of the sodium channel on the outer side of the cell membrane, is made up of protein "walls" and has an aqueous cavity similar to an irregular cylinder, where the external vestibule is located, which contains the selectivity filter and the voltage sensor. The closure gate is located in the most distal portion of the sodium channel, on the intracellular side of the cell membrane. The sodium channel inlet measures about 1.2 nm and narrows to about 0.3 to 0.5 nm at the site where the selectivity filter is located, which consists of aspartic acid, glycine, lysine, and alanine. The exact mechanism of how these channels discriminate between different cations is not known [19].

Figure 2 shows a representation of a voltage-dependent sodium channel, which is in the lipid bilayer of the cell membrane. Its four domains (D1, D2, D3, and D4) are each made up of six segments (alpha helices) that cross the entire cell membrane, emphasizing segment 4, colored in black and corresponding to the voltage sensor, which has a positive charge. On the extracellular face of the cell membrane there are two types of structures that connect the six segments, the one marked with T between segments 5 and 6 of each domain represent the site where some toxins act. The FS selectivity filter in the initial portion of the ionic pore is shown. The site where LAs act is marked with an X. This site has been highly

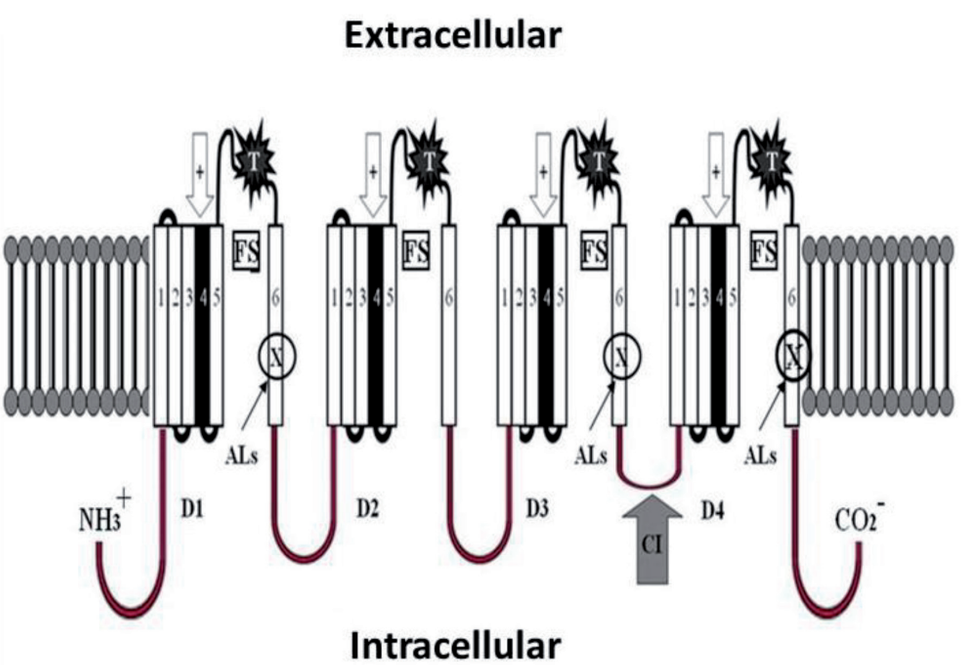


Figure 2.
Diagram of the voltage-dependent sodium channel with its 4 domains. Each domain has 6 helices that cross the cell membrane. The black stars located at the junctions of the helices 5 and 6 of each domain (pore handle) are the sites where cellular toxins (TTX) act. The sodium channel inactivation gate (IC) is located on the intracellular face between domain 3 and 4. The effector site of local anesthetics is located on helix 6 (or segment 6) of domains 3 and 4, although some schemes also draw it in domain 1.

controversial and is located in the final portion of the ionic pore near the intracellular surface of the membrane. The available information suggests that domains 3 and 4 appear to contain this point in segment 6, although some references also place it in segment 6 of Domain 1.

Among other tissues, sodium channels are located in excitable membranes such as the CNS membranes, peripheral nervous system, and the conduction system of the heart. During a nervous impulse, the cell goes through three different phases; it first depolarizes as the sodium channels open, then a refractory period follows until the cell finally repolarizes when the sodium channels become impermeable to Na^+. The intracytoplasmic junction between Domain III and Domain IV (CI in **Figure 2**) is responsible for this inactivation according to the "ball and chain" model.

4. Mechanism of action of LAs

As mentioned before, LAs inhibit the electrical impulse by selectively interfering with the function of voltage-dependent sodium channels by preventing the transport of Na^+ through the ionic pore of sodium ionophores, from outside to inside of the cells. When an electrical impulse reaches the excitable cell, the sodium channel opens for a millisecond and about 7000 Na^+ pass. A refractory period continues until the ionophores become impermeable to Na^+, and the membrane repolarizes again and enters a phase of inactivation, which is due to the activation of the intracytoplasmic junction between Domain III and IV. Unlike the tetrodotoxin and saxitoxin that act outside the cell membrane, LAs are temporarily fixed to the alpha helices 6 of Domains 3 and 4, which alters the voltage sensor and closes the inactivation gate, which obstructs the sodium channel and results in blockage of the initial phase of the action potential [14, 21–23].

There are two ways by which LAs reach the internal gate of the sodium channel and reach their site of action;

a. It has been postulated that LAs in their neutral, lipophilic (hydrophobic, B) form easily enter the lipid cell membrane in free form and from there contribute to the closure of sodium channels by the expansion of the cell membrane. From this location, LAs also pass into the cellular interior where they ionize and transform into their charged form (hydrophilic, BH^+), which reaches the site where they interact (segment 6 of Domains 3 and 4) in the internal gate of the sodium channel.

b. LAs in their cationic or hydrophilic form (BH^+) enter the cell cytoplasm through the sodium channels when they are open and reach their site of action by closing the sodium channel [14, 20, 23, 24]. LAs have no effect on the resting phase or on the potential threshold, although they can prolong the refractory period and repolarization.

Figure 3 illustrates these two routes of arrival of LAs to their receptor site in segments 6 of Domains 3 and 4.

Another factor that determines the action of LAs is the impulse frequency, the basis of the modulated receptor hypothesis, which suggests that these drugs bind more closely to the receptor within the ionic gate of voltage-dependent sodium channels when these are in an open or inactive state, that is in the depolarization phase, that when they are in a resting state, at which time they are separated from them. LAs that bind and dissociate rapidly such as lidocaine are little affected by this phenomenon, which is not the case with molecules such as bupivacaine,

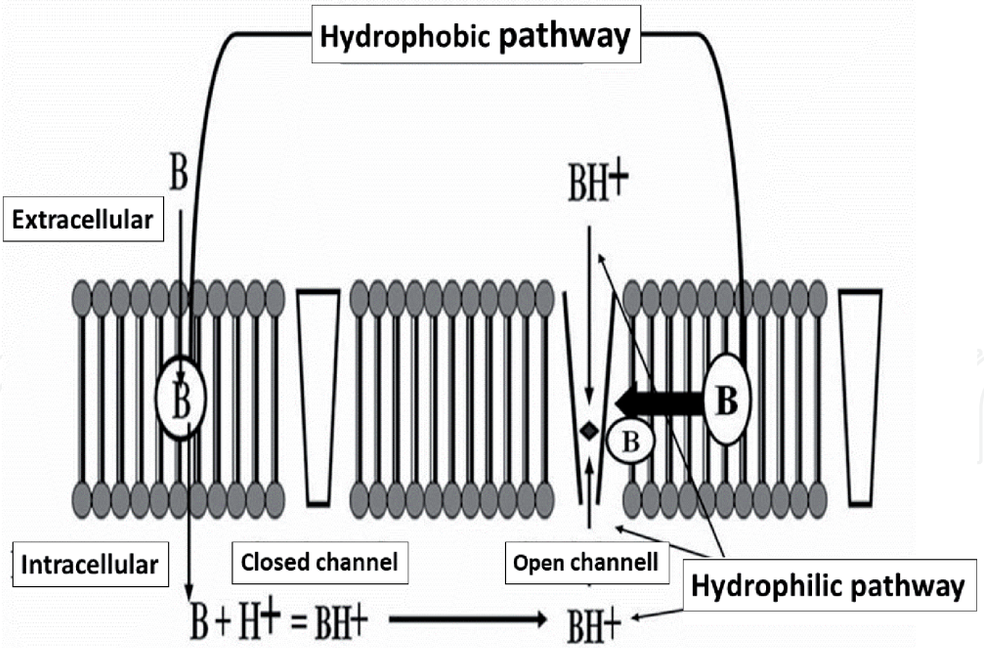


Figure 3.
Arrival pathways of LAs to the sodium channel. The hydrophobic pathway refers to the passage of LAs in their neutral (lipophilic) form that easily penetrate the cell membrane. Once in the cell membrane, the LA (B) expands it and by mechanical effect closes the sodium channel. This same neutral form of LA penetrates the cell, where it is protonized by incorporating an H+, (BH+ cationic form) that easily reaches the internal gate of the sodium channel and attaches to segment 6 of domains 3 and 4, activating the closure of the sodium channel. The hydrophilic pathway exemplified in the right portion of the scheme illustrates how a cationic LA (BH+) penetrates through and is fixed in the sodium channel.

ropivacaine, or etidocaine that are benefitted when the stimulation frequency is high, since it does not give time to recover to their resting state. This phenomenon explains the greater toxicity of some LAs [24, 25].

The affinity of LAs for the sodium channel is what determines their pharmacological action and also their toxic effects. The most important clinical outcome of these events at the level of voltage-dependent sodium channels and their interaction with LAs molecules are two results: regional anesthesia-analgesia and/or deleterious toxic effects.

5. Chemical structure of LAs

LAs are divided into two groups according to their chemical structure: the amino esters (cocaine, procaine, chloroprocaine, and tetracaine) and the amino amides (lidocaine, bupivacaine, mepivacaine, ropivacaine, and prilocaine). The typical molecule of a LA consists of three components: a) an aromatic lipophilic ring, usually benzene, b) an amphipathic intermediate chain of about 6 to 9 Å, and c) a terminal tertiary amine, hydrophilic, which is a base proton acceptor (H^+). The intermediate chain binds the basic amine with the aromatic ring and has an ester (CO)- or amide (CNH)-type bond. Each of these three parts of the LA formula contributes to different properties. The aromatic ring of the molecule improves the liposolubility of the compound that can be increased by aliphatic substitutions at certain sites (R). When the liposolubility of LAs is increased, its diffusion is increased through nerve structures (nerve sheaths and axonal membranes), which improves their anesthetic and toxic potency since a greater proportion of the drug enters the neural tissue and is fixed there with higher affinity. An example of this phenomenon is bupivacaine which has greater potency than lidocaine; the first

is prepared at 0.5% (5 mg/mL) and the second at 2% (20 mg/mL). The terminal amine may exist in tertiary form (3 junctions) that is liposoluble and facilitates cell membrane penetration, or as a quaternary form (4 junctions) that is positively charged and makes the molecule water soluble, which makes it difficult to pass through the lipid membranes [11, 25].

As stated before, the aromatic ring determines the degree of lipoafinity of the LA, and the terminal amine acts as an *on-off switch,* allowing the LA to exist as either lipoafin or water soluble. Both the tertiary and quaternary forms play a very important role in the sequence of events that lead to nerve conduction blockage. The tertiary hydrophilic amine, which is kept charged to the physiological pH and gives it its condition of weak bases with a positive charge, is the part that will be fixed to the receptor in the sodium channel of the cell membrane to exert the pharmacological effect. The presence of an ester or amide group in the intermediate chain provides the basis for their classification and also determines the metabolism of these substances. LAs with ester binding are readily hydrolyzed in the plasma by cholinesterase; instead, those with an amide junction are biotransformed by liver microsomes via the microsomal system. **Figure 4** shows the elementary chemical structure of LAs.

If the size of the molecule of a LA is increased, its potency and duration of action increase but also its toxicity. There is a direct correlation between potency, duration of effect, lipophilic character, molecular size and toxicity. Chloroprocaine is the least toxic, followed by procaine, prilocaine, lidocaine, mepivacaine, etidocaine, ropivacaine, bupivacaine, tetracaine and dibucaine, with cocaine being the most toxic LA.

Another aspect of capital importance is the stereoisomerism that some LAs have. It refers to the existence of molecules with the same structural and molecular formula, but with different spatial orientation around a particular atom, the chiral center. It is like a reflection in a mirror, like placing one hand next to the other; they are the same but cannot be superimposed, they are mirror images. LAs of the pipecoloxylidide family (mepivacaine, bupivacaine and ropivacaine), as well as etidocaine and prilocaine are chiral compounds, with an asymmetric carbon atom, which can exist in their enantiomeric form, such as mirror images. When the compound deflects the polarized light to the left it is an S-isomer (Sinus) or levo-isomer, if the light is rotated to the right it is an R-isomer (Rectus) or dextro-isomer. Although the S and R isomers have a similar pharmacological activity, the clinical importance of the isomerism is that the same drug can have different biological activity. For example, the S-enantiomers of amino-amide LAs produce greater vasoconstriction and have less systemic toxicity than D-isomer. The typical example of stereoisomerism is

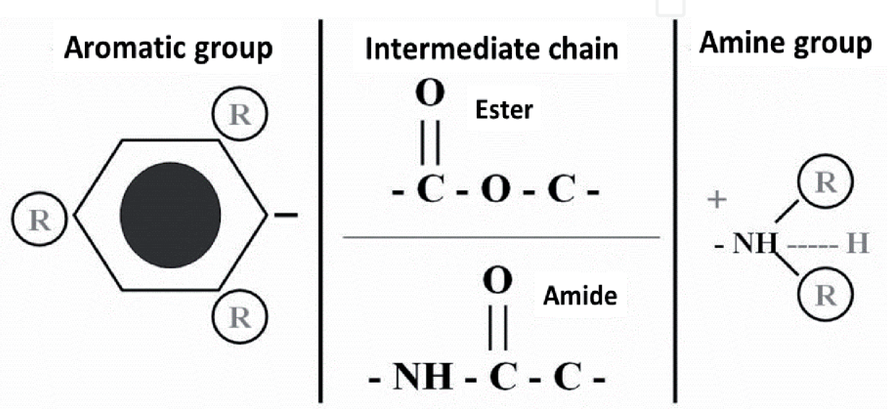


Figure 4.
Typical structural formula of a local anesthetic.

Amino ester	Amino amide
Cocaine	Dibucaine
Benzocaine	Lidocaine
Procaine	Mepivacaine
Tetracaine	Prilocaine
2-cloroprocaine	Bupivacaine
	Etidocaine
	Ropivacaine
	Levobupivacaine

Table 2.
Chemical classification of local anesthetics.

bupivacaine, which contains the dextro-isomer and levo-isomer. The mixture of both is known as racemic combination. Ropivacaine only has a L-isomer. Lidocaine and ametocaine are aquirales since they do not have stereoisomers. D-isomers have more affinity for sodium channels than L-isomers, this makes the former more toxic [26, 27]. **Table 2** shows the chemical classification of LAs.

6. Physical properties, activity, and potency

LAs are small molecules 220–350 Daltons weight, weak bases, poorly soluble and unstable in water, and therefore, they must be combined with a strong acid to obtain a stable salt that is soluble in water at pH 4.7. The solubility in water is directly related to the degree of ionization and inversely related to the fat solubility. In solution, LAs exist in two forms: basic, nonionized (B) and acidic, cationic, ionized (BH^+). The ratio between these two forms depends on the dissociation constant (Ka) of the conjugated acid and on the local concentration of H^+ ions. At a specific pH for each LA, the concentration of B is equal to that of BH^+. This pH is called pKa. The relationship can be expressed like this: pKa = pH-log (B) / (BH^+). At a pH of 7.40, the percentage of BH^+ form will be higher the higher the pKa. Diffusion of a LA is passive. In order to act they must contact the axon and for this they must pass through the epineurium, perineurium and endoneurium of the peripheral nerve, as well as the myelin layer in the myelinated fibers (lipid-rich structures), and finally cross the cell membrane to be in contact with the receptor site on sodium channels. The fat-soluble basic form B diffuses easily through the perineural structures and the axonal membrane; once inside the cell it is protonized and it is this ionized form that occupies the aforementioned receptor site [23, 25].

The minimum inhibitory concentration (MIC) is necessary to block the conduction of a nerve impulse along a nerve fiber within a certain period. The MIC is different for each LA and allows to differentiate them according to their potency. Several factors can determine the Cm: the size of the fibers (higher MIC for the thicker ones), the pH (lower MIC at higher pH), calcium concentration (higher MIC at higher calcium concentration), and frequency of nerve stimulation (smaller MIC at higher frequency).

Due to the characteristics of the nerve fibers, LAs first block the unmyelinated fibers (C fibers, which correspond to the postganglionic neurons of the autonomic nervous system), those of nociceptive conduction (analgesia), proprioceptive, tactile sensitivity, and pressure (anesthesia), and finally, the motor fibers (motor block).

The latency period of a nerve block is not linked to the potency of the LA, but seems to depend on its lipid solubility and pKa, that is, on the pH in which 50% of the molecules are in ionized form and 50% in nonionized form. The higher the pKa, the greater the latency time of a LA. On the other hand, the decrease in tissue pH can lengthen the latency time by limiting the formation of free base; instead, carbonation of a LA solution shortens its latency time. Alkalinization has also been shown to produce a better sensory and motor quality nerve block and may increase diffusion of block height. By alkalinizing LAs, their ionization increases and the percentage of fat solubility of the LA increases, facilitating its diffusion through the lipid structures of the nerves, including the axonal membrane. The addition of 1 mL of sodium bicarbonate to 10 mL of lidocaine improves the onset of extradural or peripheral block for 3–5 min, also increasing its duration of action.

With the exception of cocaine and ropivacaine, LAs produce vasodilation. Adding a vasoconstrictor to LAs is an acceptable routine since two basic actions were demonstrated: increased duration of action and decreased absorption. It also increases the intensity of sensory and motor block in neuroaxial anesthesia. Epinephrine was one of the first drugs to be injected into the subarachnoid space: however, its use was not widespread as the initial results were disappointing. The local vasoconstriction produced by adrenaline favors the decrease in the absorption of LAs, which favor a longer interaction, in addition to decreasing blood concentrations levels and thus their potential for systemic toxicity. On the other hand, epinephrine has an effect on alpha$_2$ receptors in the CNS, especially in the spinal cord, which could be another factor for the improvement it has in neuroaxial blocks. Higher concentrations of adrenaline 2: 000,000 (5 μg/mL) do not offer major advantages in terms of prolonging anesthesia or reducing plasma concentrations. Never use solutions with adrenaline to infiltrate areas with terminal arterial circulation such as the fingers, the penis, the nasal tip, or other areas with critical arterial circulation, since it may promote ischemia and local necrosis.

	Physico-chemical characteristics				Relative potency in different blocks		
Anesthetic	**pKa**	**Ionized % at pH 7.4**	**Partition coefficient**	**% protein binding**	**Epidural**	**Spinal**	**Peripheral nerve**
• Bupivacaine	8.1	83	3420	95	4	9.6	3.6
• Levobupivacaine	8.1	83	3420	97	4	9.6	3.6
• Etidocaine	7.7	66	7317	94	2	6.7	0.7
• Lidocaine	7.9	76	366	64	1	1	1
• Mepivacaine	7.6	61	130	77	1	1	2.6
• Prilocaine	7.9	76	129	55	1	¿	0.8
• Ropivacaine	8.1	83	775	94	4	4.8	3.6
• Chloroprocaine	8.7	95	810	—	0.5	—	—
• Procaine	8.9	97	100	6	—	—	—
• Tetracaine	8.5	93	5822	94	—	—	—

**Modified from Salinas FV, Liu SL, Schlz AM. Analgesics. Ion channel ligands/sodium channels blockers/local anesthetics. Chapter 30. In: Evers AS, Maze M. Editors. Anesthetic pharmacology. Physiologic principles and clinical practice. Editorial Churchill-Livingstone. Philadelphia, USA. 2004 pag 507–537.*

Table 3.
*Physical and chemical characteristics and relative potency of some local anesthetics **

The phenomenon of tachyphylaxis or acute tolerance to LAs is characterized by a decreased effectiveness of a LA with repeated administration of the same dose. Its prevalence and mechanisms have not been well defined. This phenomenon occurs with different anesthetics, with different application techniques, and has been seen to develop more frequently when redosing is administered after the analgesic effect of the previous dose has ended [28, 29]. It has been mentioned that it could be due to a progressive acidification of the injection site that is established more rapidly with weak pKa LAs. A central mechanism through spinal cord sensitization that could be avoided by pretreatment with NMDA or nitric oxide antagonists has also been described [29–31].

The potency of LAs refers to the sensitivity of the neural tissue to the different LAs. This potency increases with increasing affinity for lipids. The binding capacity of LAs to the phospholipid membrane as a result of the physicochemical characteristics and the interaction in vivo is directly related to their potency. Other factors affecting the potency of a LA include: hydrogen ion balance, fiber size, type, and myelination, vasodilator/vasoconstrictive properties (affects vascular absorption rate), frequency of nerve stimulation, tissue pH, and electrolyte concentrations (hypokalemia and hypercalcemia antagonize the block).

Table 3 shows some physical and chemical characteristics as well as the relative potency of some frequently used LAs.

7. Pharmacokinetics

The anesthetic and analgesic results of the injection of a LA in the vicinity of the neural tissue depend on the factors that have already been described. Plasma levels are affected by the injection site, the degree of absorption, its tissue distribution, its metabolism, and elimination, among other factors that have already been discussed.

7.1 Absorption

The quantity of LA that is absorbed from its application site and reaches the bloodstream is an important toxicity and elimination factor. LAs with poor absorption are safer. The absorption depends, on one hand, on the characteristics of the tissue; it increases in very vascularized territories and diminishes in fatty tissue. The plasma concentration depends on the total dose administered rather than the concentration, for most LAs there is a linear relationship between total dose and blood concentration [32]. On the other hand, the physicochemical characteristics also modulate the absorption of the drug, for example, the most lipophilic LAs and with greater affinity for proteins will be absorbed more slowly than those with less affinity for fatty tissue. Remember that the most lipophilic are also the most potent LAs. The decrease in absorption when adrenaline is added is more effective for LAs of short action and lower potency [33, 34]. With this, gradual absorption is achieved, the duration of action is prolonged and plasma levels are decreased as well as hemorrhage in the operative field.

7.2 Distribution

It depends on the physicochemical characteristics of each LA, its coefficient of solubility and plasma protein binding. A higher coefficient of solubility together with a lower degree of protein binding favors an easier distribution in peripheral tissues and a lower plasma concentration. LAs cross the blood-brain and placental

barriers by simple diffusion; this diffusion is greater when the ability to bind to plasma proteins is lower. Variable levels bind to plasma proteins in the bloodstream, particularly alpha-1- glycoprotein acid. This protein-binding property correlates with its affinity for sodium channels and predicts the duration of neural blockage. Bupivacaine has the highest percentage of protein binding and is therefore the LA with the longest duration of action.

7.3 Metabolism and elimination

LAs differ in their metabolism according to their chemical structure; those with ester-type binding (except cocaine) are rapidly hydrolyzed by plasma esterases, so the duration of their action increases with the deficit of this enzyme or the presence of atypical cholinesterase. Cocaine is hydrolyzed in the liver. The metabolites of the esters are eliminated by the kidney.

Amide LAs are metabolized in the liver. This is a slow process, which favors a longer half-life than esters and can accumulate when repeated doses or infusions are administered. Liver function interferes with the elimination of these drugs; extraction, perfusion and hepatic metabolism are definitive factors, as it is the degree of protein binding. The metabolites and the nonmetabolized drug are eliminated by urine and a small amount by feces. Elimination is favored by an acid urinary pH. Prilocaine is metabolized outside the liver.

The fact that amino ester-type LAs are rapidly metabolized favors that they remain in the blood for a short period of time, including placental blood and the fetus. Those of the amino-amide type pass more easily to the fetus, especially those with lower affinity to plasma proteins such as lidocaine, which can result in fetal toxicity. When the fetus has been compromised by any pathology and is acidotic, more ionization of the LA that has passed into its fetal circulation is favored. In this way the LA will remain longer in the fetus with the possibility of severe toxicity. In the newborn, this toxicity can be accentuated since there is no hepatocellular maturity.

8. Clinical aspects

LAs are one of the most commonly used drugs in clinical anesthesia; either by the neuroaxial route, in the vicinity of nerves and nerve plexuses, subcutaneous, transcutaneous, trans mucosal, intraarticular, and intravenously. The introduction of levoisomeric LAs, the evolution of regional anesthesia techniques with the recommendations of epidural test dose with a vasoactive marker, fractional peridural doses, low and intrathecal minidose, multiple injections with low volumes for nerve plexuses blocks, the use of nerve stimulator, guides with ultrasound and other imaging techniques, as well as the addition of adjuvant drugs such as opioids, alpha$_2$ agonists, NMDA receptor antagonists, among others have done regional anesthesia safer. **Tables 4** and **5** categorize the most important formulas and characteristics of LAs most commonly used in anesthesiology.

8.1 Amino ester LAs

The precursor of this group is cocaine. They are characterized by being metabolized by plasmatic esterases, short half-life and being related to allergic reactions. The most commonly used are procaine, chloroprocaine, and tetracaine. Benzocaine has no use in regional anesthesia.

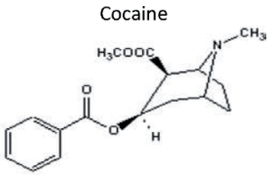
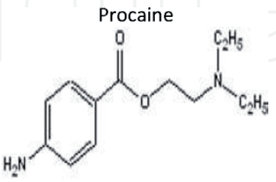
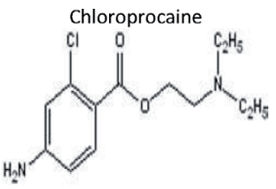
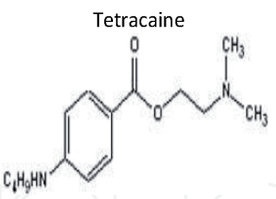
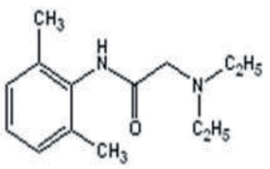
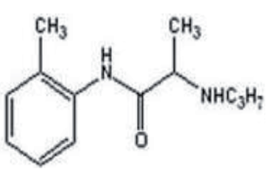
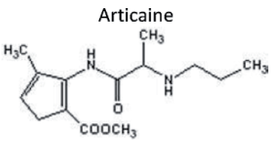
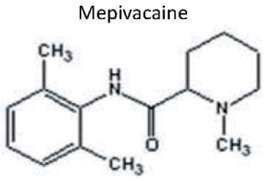
Formulae	Important features
Cocaine 	In addition to blocking the impulse of axonal conduction, it has the ability to inhibit neurotransmitter recapture in adrenergic neuronal endings, which means accumulation of norepinephrine in sympathetic synapses inducing vasoconstriction and cardiac stimulation. In the CNS, the accumulation of norepinephrine causes stimulation; however, some adrenergic neurotransmitters in the CNS are inhibited, in particular the dopamine recapture resulting in euphoria and abuse potential. Its clinical utility is limited to topical anesthesia, in solutions 4 and 10%. Due to its vasoconstrictor action, it has been used in anesthesia of the nasal mucosa to facilitate nasotracheal intubation.
Procaine 	It has been used at 0.5, 1, 2, 5, and 10% for infiltration, peripheral, and spinal blocks. Procaine is of special interest in dentistry in 2% solution with 1:50,000 adrenaline. The allergic capacity of para-aminobenzoic acid (PABA) limits its clinical utility. The maximum doses are 750 mg with adrenaline and 500 mg without vasoconstrictor. It has been used by the subarachnoid route in increasing concentrations to establish the differential diagnosis in some painful syndromes.
Chloroprocaine 	It is used in solutions 1, 2, and 3% for infiltration, peripheral blockages, and epidural anesthesia. Due to its brief time of action, it is very useful in peridural block in cesarean section. The neurotoxicity observed after intrathecal injection, attributed to the sodium bisulfite in the solution, has limited the wide use caused by its low systemic toxicity. The maximum recommended doses are 800 mg with adrenaline and 600 mg without it. There are studies that favor intrathecal injection of chloroprocaine without methylparaben.
Benzocaine 	Useful in topical anesthesia in the form of ointment, chewable tablets, and gel. It is poorly soluble and remains in the place of its application. It is not used in regional anesthesia.
Tetracaine 	It has pKa of 8.46, plasma protein binding of 75.6% and N-heptane / water partition coefficient of 4.1. Despite its high systemic toxicity, it has been used in subarachnoid anesthesia in hyperbaric solutions 1 and 2% due to its high efficacy. Its latency is not very long, and the duration of the anesthetic effect is 2 to 3 hours, because its plasma hydrolysis is quite slow. Its use has been replaced by levoisomeric anesthetics.

Table 4.
Formulae and characteristics of amino ester local anesthetics.

8.2 Amino amide LAs

They are the most used in regional anesthesia. Lidocaine is the typical anesthetic with which almost all new drugs in this group have been compared. Even when they have differences such as latency time, duration, and toxicity they have a mechanism of action common to all LAs. They can be divided into two large groups: those of short duration and those of long duration.

Slow long-release of LAs are recent advances that have improved the management of postoperative pain. Nanostructured carriers, such as liposomes and polymers, facilitate the prolonged release of LAs. Exparel® was the first approved liposomal LA to combine racemic bupivacaine with liposomes. Polymersomes have advances over liposomes with complementary profiles, inspiring the emergence of hybrid carriers [35, 36]. Also, multilamellar vesicles with ropivacaine are being investigated to prolong its analgesic effect [37].

Formulae	Most important features
Lidocaine 	It is the prototype in this group. After intravenous administration, the apparent volume of distribution is 92 L. Its alpha half-life is 8.3 min, its beta half-life is 108 min, and its plasma clearance 0.77 L/min. Its metabolism is hepatic, with an extraction coefficient of 0.7. The addition of adrenaline decreases its passage to the blood by 30%. It has a duration of action that varies from 2 to 3 hours depending on the site of administration and the addition of adrenaline. The toxic neurological manifestations of lidocaine are directly proportional to plasma levels. If these are low (0.5 to 4 mg / mL); lidocaine is anticonvulsant, at higher levels (8 mg/mL) it can cause seizures. In the heart, lidocaine blocks sodium channels, decreasing contraction (V max), the amplitude and duration of the action potential, and increases the duration of the refractory period. These effects are only observed with elevated plasma levels. The action on the heart can be summarized in: dose automatism: below 5 mg/mL, onset of sinus bradycardia; conduction: no modification (atrioventricular or intraventricular) at usual doses; contractility: decrease, but only at doses that cause frank toxicity. At low plasma levels, lidocaine increases vascular tone; at higher levels vasodilation occurs. Direct intravascular injection does not produce obvious hemodynamic alterations as long as the dose is not greater than 3 mg/kg. From 4 to 8 mg/kg, cardiovascular depression occurs, which is dangerous if the dose is greater than 8 mg/kg. If there is heart failure, the toxicity threshold decreases.
Prilocaine 	Its pharmacokinetic properties are similar to those of lidocaine, although it is less vasodilator. It is used in infiltration for peripheral nerve and in epidural anesthesia. The usual concentrations range between 0.5 and 2%. It is 40 times less toxic than lidocaine. An ideal use is intravenous regional anesthesia. A potential risk is the appearance of methemoglobinemia (total doses greater than 500 to 600 mg), so its use in obstetrics is restricted or contraindicated.
Articaine 	First approved in Germany in 1976, in Canada in 1982 and in 2000 by the FDA. It has a thiophene group, an ester group and also an amide group. It has been classified in the amide group by its intermediate chain and because it is metabolized in the liver. However, its ester portion allows it to be degraded by plasma pseudocholinesterase. The mean maximum plasma drug concentration is about 400 μg/L for articaine with epinephrine 1:200,000 and 580 μg/L without epinephrine. The elimination half-time is approximately 20 min. The rapid breakdown to the inactive metabolite articainic acid is related to a very low systemic toxicity and consequently to the possibility of repeated injections. It has been associated with paresis and long-lasting paraesthesia, which are more frequent than those produced by lidocaine. It is commonly used in dentistry.
Mepivacaine 	Its molecular formula is C15H22N2O-HCL, soluble in water and very resistant to acid and alkaline hydrolysis. It is available in concentrations of 1%, 1.5% and 2%. The latency and duration of action are similar to those of prilocaine and its potency resembles lidocaine. Useful concentrations range between 0.5 and 2%. It diffuses well through tissues, which allows favorable blocking despite a less optimal needle placement. It produces an intense motor block. It is used to perform infiltration, peridural and spinal anesthesia (with a lower incidence of neurological alterations than lidocaine). Its use is not advised in obstetrics based on its prolonged metabolism in the fetus and in the newborn. It is recommended for peripheral nerve blocks in certain conditions: patients with cardiac risk or with drugs that potentiate toxicity. Adrenaline decreases the absorption of mepivacaine but does not prolong its duration of action.

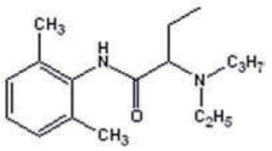
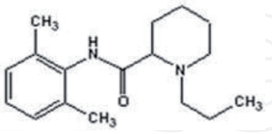
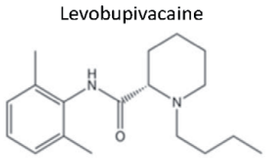
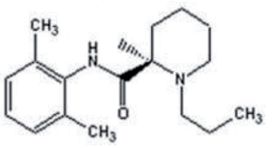
Formulae	Most important features
Etidocaine 	It is more fat-soluble and has a higher degree of affinity to plasma proteins than lidocaine, has a short latency and longer duration. Epidural route is used at 0.5 to 1%. It produces greater motor blockage than sensitive which makes it useful in abdominal surgery, its use in obstetric analgesia anesthesia is not advised. Its beta half-life is 2.5 hours, and care should be taken in liver disorders because of the prolonged action.
Bupivacaine 	It is a racemic mixture, long-acting drug that produces a differential sensory-motor block at low concentrations. It has a limited placental transfer, so it is widely used in obstetrics in concentrations of up to 0.5%. Higher concentrations are not recommended in obstetrics. It is the LA with greater cardio and neuro toxicity and greater difficulty in resuscitation since it has a great affinity for voltage-dependent sodium channels. However, after lidocaine, it is the most used. It is widely used in pain clinic.
Levobupivacaine 	It is bupivacaine levoisomer. It has pharmacological properties similar to bupivacaine but less toxicity. Its toxicity depends on the route of administration and the dose, its pharmacokinetic is similar to bupivacaine and its plasma peak is 30 min after epidural administration, with an alpha-glycoprotein and albumin binding greater than 97% at concentrations of 0.1 at 1 ug/mL. It is metabolized in the liver and the kidney does not seem to intervene in its elimination. Produces differential blockade similar to bupivacaine, which depends on the dose and concentration, which will be less than 0.25% such as 0.0625 and 0.125% for epidural analgesia, and 0.5% to 0.75% for neuroaxial anesthesia and peripheral nerve blocks.
Ropivacaine 	The first levoisomeric LA for clinical use. The plasma alpha glycoprotein binding is 95%, with a pKa of 8.1 and a partition coefficient of 141. Due to its low absorption, it has a longer elimination half-life and its pharmacokinetic has a linear proportional to the dose, with a volume of distribution of 47 liters. Like bupivacaine, it has a greater effect on C fibers than A, which produces a sensory rather than motor block. The clinical experience is excellent in neuroaxial anesthesia and peripheral nerve blocks. It is of great value by epidural route (obstetrics), and in postoperative analgesia. It is characterized by a block of greater latency and long duration. Less analgesic potency than bupivacaine and levobupivacaine. It is less cardiotoxic and neurotoxic than bupivacaine with a better response to resuscitation. Usefull in pain clinic.

Table 5.
Formulae and characteristics of local amino-amide type anesthetics.

8.3 There are 3 LAs: articaine, sameridine, and centbucridine, which due to their special physico-chemical characteristics deserve a brief description

8.3.1 Articaine

It is a short-acting LA with intermediate potency. It has been included in the amide group, but it contains an additional ester group that is quickly hydrolyzed by esterases, a chemical characteristic that accelerates its metabolism. The plasma protein binding rate of articaine and articainic acid is 70%. I.V. articaine 80 mg does not produce toxic effects in healthy individuals. It has been used neuraxially, ocularly, intravenously, and in regional blocks. It is suitable and safe for procedures requiring a short duration of action in which a fast onset of anesthesia is desired,

e.g., dental procedures and ambulatory spinal anesthesia. Its most frequent use is in dentistry, where it has demonstrated efficacy and safety. Complete anesthesia is achieved in 90% of cases, using articaine 4% 60–80 mg with epinephrine 1: 200,000. It diffuses well through soft tissue and bone; concentration in the alveolus of a tooth in the upper jaw after extraction was about 100 times higher than that in systemic circulation. In comparative clinical trials, its effects were not generally significantly different from those of other short-acting LAs like lidocaine, prilocaine, and chloroprocaine. There is no conclusive evidence demonstrating above average neurotoxicity, although cases of frequent persistent paresthesia after articaine use have been described [38–41]. Saralaya et al. compared 4% articaine with 1:100,000 epinephrine versus 2% lidocaine with 1: 100,000 epinephrine in 50 patients operated on the third molar. These authors found that the mean onset time for articaine and lidocaine was 3.16 ± 0.55 and 3.2 ± 0.48 min, respectively. Postoperative analgesia was longer in the articaine group and its duration of action was 289.04 ± 40 and 361.88 ± 40 min, respectively, compared to lidocaine, which is 144.2 ± 12 and 197.44 ± 25 min, respectively. These authors recommend articaine since it was more potent and with a longer duration of action with better postoperative analgesia and could be considered as an alternative to lidocaine [42]. Even in the presence of pulpitis, articaine proved to be more effective than lidocaine in patients undergoing root canal treatment [43]. There is no information available on the use of articaine during lactation, so its use is not entirely recommended yet.

8.3.2 Sameridine

This drug has mixed characteristics: LA and μ-opioid partial agonist. It is structurally similar to meperidine. It is a compound that is still under investigation (N-ethyl-1-hexyl-N-methyl-4-phenyl-4-piperidine carboxyamide hydrochloride) mainly for spinal anesthesia. Liver hydroxylation is the primary metabolic pathway, and no local neurotoxicity has been found in animal studies. Its effect on respiration is directly related to plasma levels. In healthy volunteers [44] 25 mg vs. intrathecal bupivacaine 15 mg has similar effects on resting ventilation. The ventilatory response to hypoxia and hypercarbia were found to be discreetly diminished in the group treated with sameridine. Intravenous doses of 0.73 mg/kg depress the ventilatory response to hypercarbia [45]. The clinical doses of 150 μg/kg have no significant effects on ventilation [46]. Intrathecal doses of 15–25 mg of sameridine are sufficient for inguinal and orthopedic surgery, respectively. Doses of 5–20 mg are comparable with 100 mg of intrathecal lidocaine. The advantage is that sameridine produces residual analgesia and reduces the need for opioids in the first hours of the postoperative period [7, 8], so it could have a role in the management of postoperative pain.

8.3.3 Centbucridine

It is a nonester, nonamide LA, chemically known as 4-N-butylamino-1,2,3,4-tetrahydroacridine hydrochloride. It is a quinolone derivative drug with LA effects synthesized in 1982 by Patnaik et al. [47–49]. It is 5 to 8 times more potent than lidocaine, while its LD50 is one fourth that of lidocaine. It has vasoconstrictor and antihistamine effects, rapid onset of action (1–3 min), duration of action is prolonged (2.5 hours), and no events of cardiotoxicity or neurotoxicity have been reported. Centbucridine has been investigated for infiltration, conjunctival surface, in peripheral nerves, neuroaxial anesthesia, intravenous regional anesthesia; however, the majority of studies are in dental anesthesia [9, 50–52]. Most studies compare 0.5% centbucridine vs. 2% lidocaine, with similar anesthetic results,

although some have found longer anesthetic duration in patients who were treated with centbucridine [51, 53]. Centbucridine can be used with confidence in dental patients who cannot tolerate other LAs or when epinephrine is contraindicated.

8.4 Maximum dose of LAs

Another clinical aspect of capital interest is the maximum doses of each LA. The maximum recommended doses have been established arbitrarily by the pharmaceutical industry [54] and vary according to the route of administration, the type of anesthetic, with or without vasoconstrictors, as well as the type of patient and surgery. **Table 6** shows the maximum recommended doses for the most commonly used LAs, without these doses having been established by studies conducted specifically to determine the safest and most effective amounts of each. Note the variants, sometimes with important ranges; 200 mg of lidocaine is recommended in Europe, while in the United States this dose reaches 300 mg when epinephrine is not used. Notwithstanding these differences, it is advisable to stay below the maximum recommended dosage range to avoid undesirable toxic effects.

8.5 Adequate anesthetic technique

Regional anesthesia techniques are important not only in the expected results, but to reduce undesirable side effects of LAs. It is known that spinal anesthesia produces lower plasma concentrations of LAs, unlike interpleural injection that in theory results in higher concentrations, and therefore, could be the procedure that produces more toxic events. However, this situation is hypothetical, since toxic events occur more frequently in peripheral blockages and peridural injections. For different types of nerve blocks, the same total injected dose produces different blood concentrations for mepivacaine, lidocaine, prilocaine and etidocaine, with the intercostal block being the one that produces the highest blood absorption, followed by injections in the peridural space. Plexus nerve blocks and subcutaneous injection are those that have a lower degree of absorption of LAs.

8.6 Undesirable side effects

The anesthetic and analgesic effects of LAs and their toxicity originate in the same mechanism of action; its interaction in the sodium channels. The therapeutic efficacy and safety of LAs has been proven from the moment of their discovery and it was precisely the deleterious effects that prompted the search for safer agents.

Maximum dose of lidocaine: Without epinephrine 200 mg (in Europe), 300 mg (in USA) With epinephrine (5 μg/mL) 500 mg in both regions
Maximum dose of PPX anesthetics: Bupivacaine 150–175 mg Levobupivacaine 150 mg Ropivacaine 200–300 mg
Epinephrine 1: 200,000 reduces absorption of subcutaneous lidocaine by 50%, intercostal, epidural and brachial by 20–30%

Table 6.
Maximum dose of LAs [54].

In 1905 Braun mentioned the characteristics that a new LA should have: *In addition to producing local anesthesia, any new drug in this abundant group should have the following properties: be less toxic than the standard available, it should not irritate or damage tissues, it must be soluble in water, and stable in solution, it must be able to mix with adrenaline, and must be rapidly absorbed into the cell membrane* [55]. More than a century of these recommendations have passed, and we still use LAs that do not meet these characteristics. LAs are used with an acceptable safety margin, without being the ideal drug. The following paragraphs briefly describe the most interesting side effects due to their magnitude and frequency. For more information on toxicity read chapter 10 of this book.

8.6.1 Toxicity

The history of LAs toxicity began at the end of the 19th century, when clinicians of that time realized the deleterious effects of cocaine and began the search for better drugs. Albright's editorial in 1979 [13] commented on six deaths due to cardiovascular collapse after the administration of bupivacaine or etidocaine whipped up this investigation in such a rapid way that currently there are safer drugs. The most important systemic toxic reactions are on CNS and the cardiovascular system. The CNS is affected with lower plasma concentrations than those that cause cardiovascular toxicity and is manifested by alterations in cognition, seizures, and coma. Arrhythmias with or without cardiovascular collapse of difficult management and death occur in the cardiovascular system. The incidence of systemic toxicity has been reduced to 0.01%, with regional blockages being the most associated with these events (7.5/10,000). The current use of ultrasound-guided nerve blocks is likely to reduce these statistics. Toxic effects can be grouped into two large groups:

1. Toxic reactions to:

    a. Systemic and local

    b. Not related to the LAs

2. Allergic reactions

    a. To the LA

    b. To conservatives or antioxidants

Events due to toxicity still occur in expert hands and are more related to the type of block and the dose injected. Various factors have been described:

- Potency of the LA. The greater the fat solubility, the greater potency and more possibility of cardio and neuro toxicity.

- Isomerism. LAs that contain a dextroisomer are more toxic than levoisomers. The former have been shown to have a higher affinity for the effector site of sodium channels.

- Total administered dose (plasma concentration). Toxicity is related to plasmatic concentration of AL, and this depends directly on the total administered dose. Epidural blocks and tumescent subcutaneous infiltrations use the highest doses of LAs and have been linked to toxic events.

- Injection site. In general terms, the blood absorption of LAs varies according to the injection site, although it is modified by factors such as the type of anesthetic injected, the addition of vasoconstrictors, and the speed and frequency of injection. The interpleural route favors high absorptions due to the large injection surface and its vascularity. However, this route has not been more frequently related to systemic toxicity, perhaps due to the lung capacity to fix and eliminate the concentration of LA up to ~40%. Spinal administration does not produce systemic toxicity from small doses and decreased vascularity. Injections close to the brain (facial, nasal, oral, neck) have larger possibility of neurological systemic toxicity, either by direct intra-arterial injection or by retrograde flow that transports small doses of the LA directly to the brain tissue than induces seizures and coma [56].

- Patient's health/ASA. Factors such as age, liver and kidney dysfunction, hypoxemia, acidosis, pregnancy, and pharmacological interactions (cytochrome P450 inhibitors) modify the possibility of systemic toxicity.

In the ester group, cocaine remains the most toxic LA, and procaine and chloroprocaine are the least potent and least toxic potency, not only in the ester group, but among all known LAs. In the amino-amide group racemic bupivacaine, etidocaine, and mepivacaine are more toxic than levobupivacaine and ropivacaine. Lidocaine and prilocaine are the least toxic in this group.

Cardiotoxicity. The toxic effects of LAs on the cardiovascular system are divided into two groups; the physiological changes that are generated with some regional anesthesia techniques and the effects that derive from the actions of these drugs on sodium, potassium, calcium channels, and beta myocardial receptors. These side effects on the cardiovascular system can be explained by the following four mechanisms:

1. Regional effect due to the blockage of sympathetic preganglionic fibers secondary to the neuroaxial injection of the LA.

2. A direct cardio depressant/arrhythmogenic effect due to sudden and elevated plasma concentrations of local anesthetic by intravascular injection or exaggerated absorption from the injection site.

3. Cardio depressant effect mediated through the CNS.

4. Systemic absorption of toxic dose can cause spinal depression and secondary circulatory collapse.

8.6.2 Neurotoxicity

The toxicity of LAs on the nervous system manifests itself in two areas; those that are triggered by high blood concentrations and are due to their action on sodium channels in the CNS, and those that are caused by the direct application of the anesthetic on or in the vicinity of neural structures, especially the injection of lidocaine in the subarachnoid space.

8.6.3 Myotoxicity

It is well known that continuous perineural injection and direct intramuscular injection of LAs have toxic effects on the striated muscle causing inflammatory

changes. These drugs act on external cell membranes and on the membranes of intracytoplasmic organelles, especially on the double mitochondrial membrane. Bupivacaine produces alterations in active intracellular oxidative metabolism by depolarizing the mitochondrial membrane and oxidation of the pyridine nucleotide. This results in the opening of permeability transition pore (PTP), a type of channel located in intracellular membranes that plays an important role in various forms of cell death. Injury mechanisms involved early and late abnormalities to cytoplasmic calcium (Ca^{2+}) homeostasis by the sarcoplasmic reticulum Ca^{2+} ATPase and cytochrome C release. All of these alterations were dependent on bupivacaine concentration and were only found in voluntary striated muscle mitochondria, while mitochondria from esophageal muscle were resistant to bupivacaine [57]. In rabbits, continuous axillary block with placebo vs. 0.25% bupivacaine, at 24 hours neutrophilic infiltration was found in the placebo group, while the group receiving bupivacaine had a large amount of eosinophils. One week later, lymphocytes, plasma cells, macrophages and fibroblasts were found with data of muscle regeneration [58]. Zink et al. [59] compared bupivacaine vs. ropivacaine and demonstrated that the former induced necrosis and apoptosis of muscle fibers, while the latter produced less severe changes in porcine skeletal muscle. These same researchers [60] confirmed their initial results that bupivacaine 0.5% is more myotoxic than ropivacaine 0.75%, by inducing irreversible myonecrosis with calcium deposits, scar formation, and muscle regeneration. The incidence of myotoxicity in ophthalmic studies was 0.77%. Inflammatory changes within a few days after exposure marked the onset of myotoxicity, and muscle degeneration continued within the first week after exposure. Recovery time in human muscles ranged from 4 days to 1 year. None partial and complete recovery was observed in 61% and 38% of patients, respectively [61]. All LAs that have been studied have a similar myotoxic potential in terms of the tissue alterations produced, but they differ in the intensity of these lesions. Bupivacaine and chloroprocaine are the most toxic and procaine and tetracaine are the ones that produce minor alterations.

8.6.4 Allergies

True allergies to LAs are rare and generally occur more with ester-type, although allergies have been reported with amino-amide LAs, including new levoisomeric anesthetics [62]. These allergies have a highly variable frequency that ranges from 1: 350 to 1:20,000 and fortunately most are trivial, although occasionally they are factors of significant morbidity and mortality. The incidence of true IgE-mediated LA allergy remains unclear and is presumed to be as low as 0.7–1%. On some occasions these reactions have been attributed to preservatives (methylparaben) or antioxidants (bisulfites) that are contained in some commercial presentations [63, 64]. When someone is reactive to a LA, they will be allergic to it for the rest of their life due to the response of mast cells that release chemical mediators that are responsible for the clinical responses in each patient. These mediators include histamine, leukotrienes, chemotactic substances, lysosomal enzymes, prostaglandins, kinins, and platelet activating factors that facilitate capillary permeation with plasma leakage in the surrounding area. The manifestations of true allergy range from mild to severe and sometimes are deadly. The faster the clinical manifestations occur, the more severe the reaction. The most frequent expression is contact dermatitis, but they can also manifest as urticaria, rash, rhinitis, bronchial spasm, angioneurotic edema, tachycardia, and hypotension and lead to anaphylactic shock. Immunoglobulin E-mediated anaphylaxis can induce respiratory failure and cardiopulmonary collapse. The treatment of true allergies to LAs depends on their severity; mild or moderate reactions disappear spontaneously. In severe reactions it

is recommended to use steroids, H1 blockers, antihistamines, or epinephrine. When there is a probable or proven history of allergy to LAs, caution should be exercised: if allergy to an ester compound is found, it should be switched to an amino-amide anesthetic, preferably one without methyl paraben or metabisulfite. When the allergy is to an amino-amide anesthetic, it is advisable to change to another anesthetic from the same group.

8.6.5 Methemoglobinemia

Prilocaine is metabolized to O-toluidine which can cause methemoglobinemia in susceptible individuals, especially when more than 500 mg is used. In pregnant women, this problem is even more critical since fetal blood poorly reduces methemoglobin. Management is with 1–5 mg of methylene blue.

8.6.6 Rebound pain

When the analgesic effect of a peripheral nerve block performed with LAs, a state of hyperalgesia known as rebound pain may occur 12–24 hours postoperatively, with intensity disproportionate for the type of the performed surgery. It has been classified as a complication of peripheral nerve blocks, the etiology of which is unknown. Several factors have been considered, including neurotoxicity of LAs, its effects on nociceptors, direct neurotrauma, the possibility of hyperalgesia induced by systemic opioids before or during the block. Its frequency is unknown, although it seems to be increasing, especially in outpatient surgery where it has been reported in up to 40%. It is a relevant complication since it hinders the postoperative evolution, disturbing sleep, increasing the opioid requirement and delaying hospital discharge. Preventive analgesia before the blockage subsides, intra-articular or intravenous anti-inflammatory drugs, and the use of adjuvants added to nerve-block or systemic solutions can reduce rebound pain [65–67].

9. Nonanesthetic uses of LAs

Some nonanesthetic (off-label) uses of LAs have been described. Although these investigations have not been precisely determined, this topic deserves a brief description.

9.1 Cough, laryngospasm, and asthma

Lidocaine has been used successfully to prevent or treat cough and laryngospasm induced during tracheal extubation, as well as in patients with asthma and chronic cough difficult to treat [68–70]. The meta-analysis of Yang et al. found that iv lidocaine decreases postoperative airway complications [71]. Nebulized lidocaine has been used with encouraging results in patients with asthma, chronic cough, and laryngospasm; doses ranging from 10 to 400 mg are a therapeutic alternative in asthma and cough that is difficult to manage [72]. Its mechanism of action has been related to the decrease in airway inflammation via downregulation of TLR2 [73].

9.2 Effects of LAs on cancer

Regional anesthesia is preferably used in oncological surgery since it does not interfere with the immune system, and the postoperative outcome of these patients is better. On the other hand, there is evidence that LAs could have direct

antineoplastic effects [74, 75]. Some malignancies have increased voltage-dependent sodium channel activity. Blocking these channels with LAs may help inhibit tumor progression [76]. Zheng et al. found an anti-melanoma activity of ropivacaine and lidocaine but not bupivacaine, via targeting small GTPases [77].

9.3 Antibiotics

Besides pain insensitivity, it has been shown that the in vitro and in vivo use of LAs have bacteriostatic, bactericidal, fungistatic, and fungicidal properties against a wide spectrum of microorganisms, this action being attributed to the interruption of the membrane permeability of microbial cells, leading to leakage of cellular components and subsequent cell lysis. Different LAs showed varying degrees of antimicrobial capacity; bupivacaine and lidocaine, for example, inhibit growth to a significantly greater extent than ropivacaine. Higher concentrations, prolonged exposure, and higher temperature correlate with a proportional increase in inhibition of microbial growth. Reducing the incidence of endophthalmitis after intravitreal injection, prophylaxis for surgical wound infections, preventing the incidence of catheter-associated infections, reducing oral biofilms in the oral mucosa, and preventing infection-causing bacteria nosocomial are some examples of antimicrobial application of lidocaine [2, 78–80].

10. Conclusions

The first LA anesthetic was derived from the plant *Erythroxylum coca*, and regional anesthesia began in 1884 when Karl Köller anesthetized the cornea of his patients for surgical purposes. Since then, a host of events, drugs, discoveries, and various anesthesia techniques have culminated in safer and more effective regional anesthesia. LAs have an impressive history of efficacy and safety in medical and dental practice, but still have deleterious effects that can—on rare occasions—cause the death of our patients. Knowing the basics of the substrates where LAs work makes it easier to understand the action mechanisms that these drugs have on voltage-dependent sodium channels. The sequence of events that occur from the choice of the patient, the preparation and injection of LAs to the production of regional anesthesia-analgesia and/or its toxic effects are complex. These physiological and pathophysiological events depend on features as varied as the structural and physico-chemical characteristics, total injected dose, injection site, adjuvant drugs, physical condition of the patient, among others. The safe practice of regional anesthesia definitely reduces catastrophes, but these disasters can appear at any time. LAs have an impressive history of efficacy and safety in medical and dental practice.

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