Chapter

Pharmacokinetics and Pharmacodynamics of Local Anesthetics

Javier Marcos Michel-Levy

Abstract

Local anesthetics are basically weak bases whose structure consists of an aromatic half connected to a substituted amine through an ester amide linkage. The pKa values of local anesthetics are close to physiological pH, both protonated and unprotonated forms are present. The individual structures confer different physiochemical and clinical characteristics. Potency is correlated to lipid solubility in vitro, but less so in vivo. The duration of action is associated with the extent of protein binding. The onset of action is related to pKa. The intrinsic vasodilator activity varies between drugs and influences potency and duration of action. Local anesthetics block nerve conduction and interact directly with specific receptor on the Na^+ channel, inhibiting Na^+ ion influx and impairing Propagation of the action potential in axons. There are some characteristics in the blocking of nerve conduction and are related to size and function of the peripheral nerves, and to the fact that a specific concentration of local anesthetics may produce a different intensity of block. Some pathological states like decreased cardiac output, severe hepatic disease, renal disease, cholinesterase activity, fetal acidosis, sepsis, etc. altered the pharmacokinetics and pharmacodynamics of local anesthetics.

Keywords: esters, amides, pKa, Na^+ channel, pH, nerve fibers kinetics, block conduction

1. Introduction

When applied locally to nerve tissues in appropriate concentrations, local anesthetics (LAs) reversibly block the action potentials responsible for nerve conduction. They act anywhere in the nervous system and in any type of nerve fiber. Therefore, a LA in contact with a nerve trunk can produce both sensory and motor paralysis in the innervated region.

The practical advantage of LAs is that their action is reversible in concentrations of clinical importance; their administration is followed by complete recovery of nerve function [1] (**Figure 1**).

LAs are drugs primarily utilized in clinical settings to induce local anesthesia. The term local anesthesia, unlike general anesthesia, is defined as loss of sensation within a confined region without loss of the patient's consciousness. LAs are purposely used to relieve pain and induce numbness during surgical procedures and are normally applied by local injection [2].

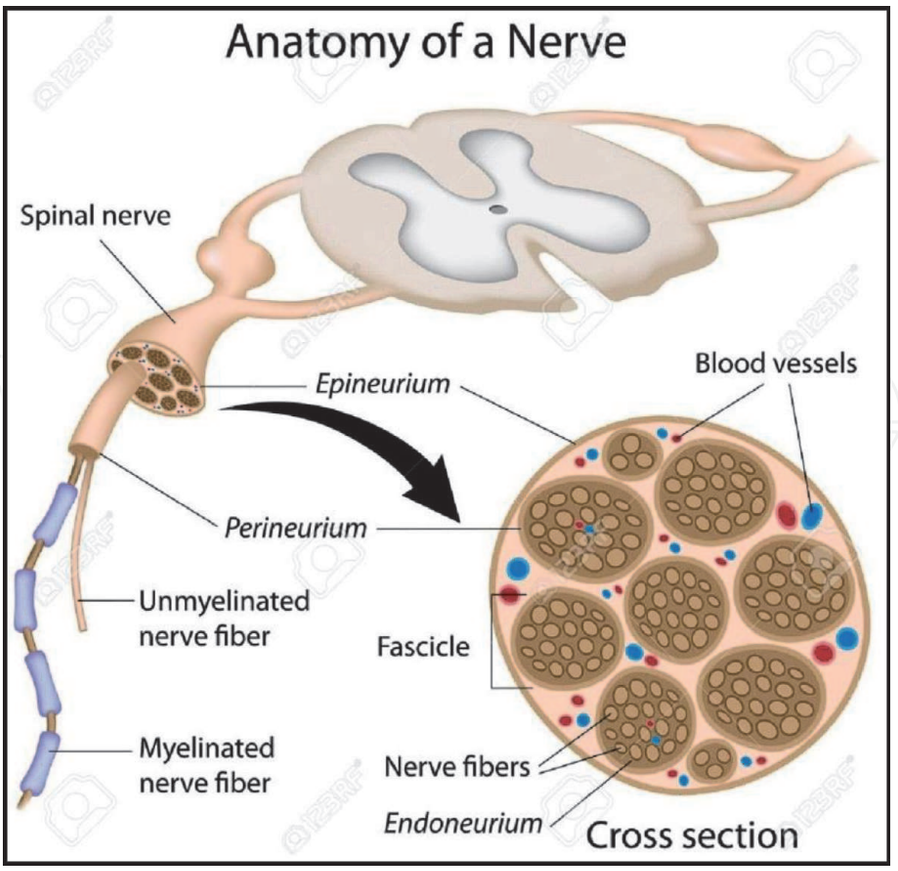

Figure 1.
Notes cards google.

2. Anatomy of the peripheral nerve

All peripheral nerves are similar in structure; neuron is the basic functional neuronal unit responsible for the conduction of nerve impulses. A typical neuron consists of a cell body (soma) that contains a large nucleus; the soma is attached to several branching processes called dendrites and a single axon. Axons vary in length and there is one only per neuron, they are a long and slender, and are also called nerve fibers; while dendrites receive incoming information and axons conduct outgoing information. Individual nerve fibers bind together, like wires in an electrical cable, and each axon is enveloped by the endoneurium (delicate layer of loose connective tissue around each axon). Groups of axons are closely associated within a bundle called a fascicle that is surrounded by perineurium (imparts mechanical strength and also acts as a diffusion barrier). Epineurium is a denser collagenous tissue that surrounds the entire nerve and holds it loosely to the connective tissue through which it travels. The paraneurium consists of loose connective tissue that keeps a stable relationship between adjacent structures filling the spaces in between them; this tissue promotes functional mobility of nerves during joint and muscular motion.

Nerves take in blood from the contiguous blood vessels along their course. These vessels that nourish larger nerves are macroscopic in bore and irregularly settled, conceive anastomoses to put on longitudinally common vessels that provision the nerve and emit subsidiary embranchments [3].

Each peripheral axon has its own cell membrane called axolemma, non-myelinated nerves such as nociceptive afferent type C fibers, and autonomous postganglionic efferent fibers contain axons coated by only one layer of cells. All large-caliber sensory and motor fibers are lined with multiple layers of myelin,

which consist of the plasma membranes of Schawnn cells that wrap themselves around the axon during growth.

Myelin considerably increases the speed of nerve conduction as it achieves that action current generated by an action potential travels through the axoplasm to the nodes of Ranvier, these are periodic interruptions of the myelin sheath, where action potentials are regenerated.

In the nodes of Ranvier of the myelinated fibers, there is a high concentration of sodium channels Na^+, which serve to propagate the impulses, although they are also observed along the axons of unmyelinated fibers.

During the transmission of an impulse, the intra and extracellular ratios of Na^+ and K^+ ions are inverted. Na^+/K^+-ATPase is stopped during depolarization and Na^+ ion perviousness increases, leaving Na^+ ions to move inside the cell and the resting membrane potential be moved. An action potential is released when depolarization enough for the membrane potential to come a threshold value, it is concerning +15 mV. During repolarization, the electrical status of the cell is restored by K^+ diffusing out of the cell, and at the end the resting membrane potential has been restored; but the cell has effectively gained Na^+ and lost K^+. However, when Na^+/K^+-ATPase is reactivated, the normal intra and extracellular ratios of Na^+ and K^+ ions are restored.

In a depolarization stream, Na^+ channels they are activated, admitting extracellular Na^+ ions influx into the cell. After that (ms), Na^+ channels inactivate. The channels get back to the initial repolarization state. The course that involves sodium channels passing from an open or closed state is called a "gate." Gate is the result of the change of polarities after a potential. It is about explaining the mode of action of

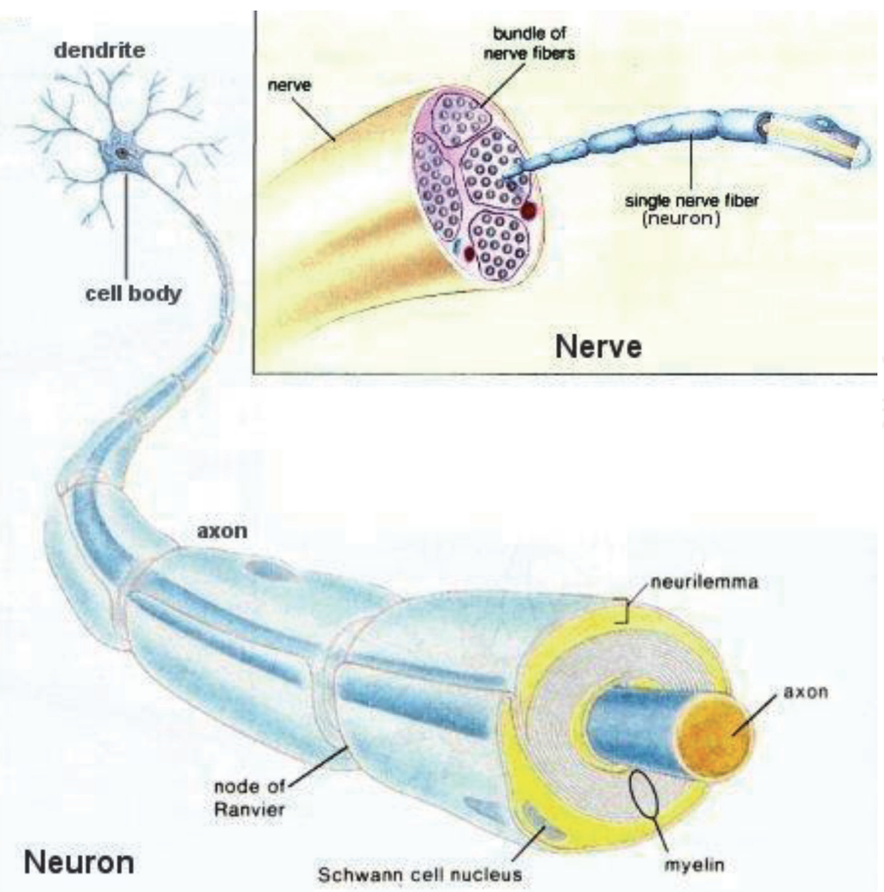

Figure 2.
Universo-review.ca free Google.

Fiber type	Function	Myelinated	Diameter (mm)	Conduction velocity (m/s)	Spike duration (ms)
Aα	Proprioception, somatic motor	Yes	12–20	70–120	0.4–0.5
Aβ	Touch, pressure	Yes	5–12	30–70	0.4–0.5
Aγ	Motor to muscle spindle	Yes	3–6	15–30	0.4–0.5
Aδ	Pain, cold, touch	Yes	2–5	12–30	0.4–0.5
C	Pain, temperature (dr) mechanoreception, reflex responses	No	0.4–1.2	0.5–2	2
B	Preganglionic autonomic	Yes	<3	3–15	1.2
C	Postganglionic sympathetic	No	0.3–1.3	0.7–2.3	2

Table 1.
Fiber type.

these channels, with the presence of voltage-dependent doors in the light of the same (**Figure 2**).

The currents of depolarization and repolarization move longitudinally along the nerve membrane and result in conduction of the nerve impulse. In unmyelinated nerves, the impulses spread at speeds of about 2 m/s. In myelinated nerves, the depolarization current jumps from node to node; this phenomenon, known as saltatory conduction, increases conduction velocity to around 120 m/s and is highly energy-efficient [4].

Neurons can usefully be classified according their diameter and speed of conduction (**Table 1**).

3. Local anesthetic molecule

The local anesthetic molecule consists of three components: (a) lipophilic aromatic ring, (b) intermediate ester or amide chain, and (c) terminal amine. Each of these contributes distinct properties to the molecule [5].

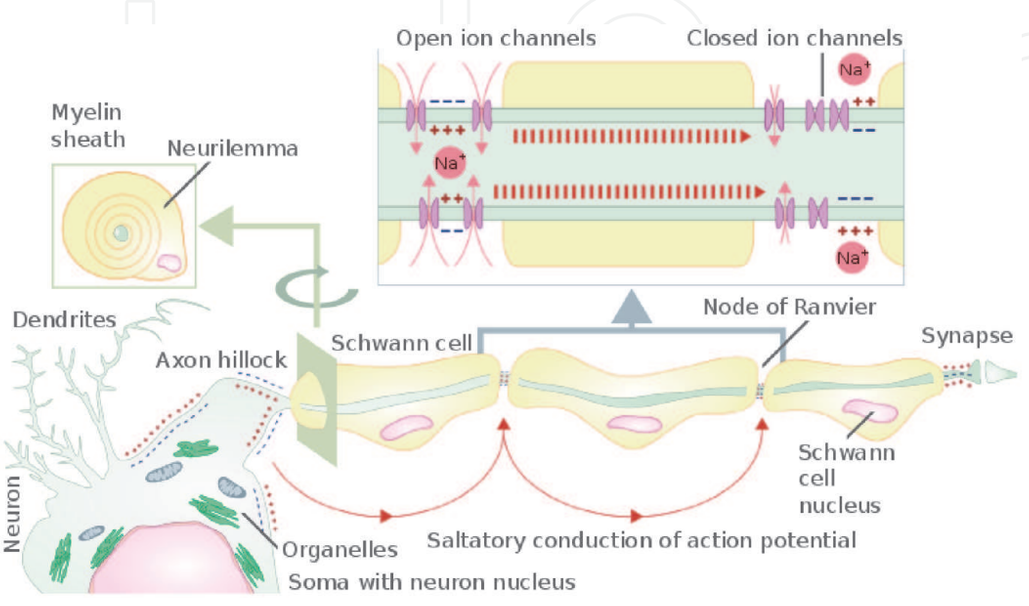

Figure 3.
Saltatory conduction. Wikiwand free Google.

In this way, local anesthetics can be classified into two groups: aminoesters and aminoamides. The aromatic ring provides a lipophilic character to the portion of the molecule in which it is found, while the tertiary amine end is hydrophilic, because it is protonated and has a positive charge in the physiological pH range [6] (**Figure 3**).

The ester-type LAs include benzocaine, procaine, cocaine, and tetracaine. The amide-type LAs include mepivacaine, lidocaine, ropivacaine, bupivacaine, and etidocaine. Lidocaine and bupivacaine are the most commonly used LAs, both are amide-type compounds, which are much more resistant than ester-type compounds to hydrolysis (**Table 2**).

In addition to the intrinsic binding affinities of LA drugs to the Na^+ channel, other variables also strongly influence the relative duration of local anesthesia; these include the volume, concentration, lipophilicity, pKa, pH, repeated injections, the presence of vasoconstrictors, and the precision of drug injection.

3.1 Hydrogen ion concentration

LAs in solution maintain a rapid chemical equilibrium between the basic uncharged form (B) and the charged cationic form (BH^+), the ratio of the two states is given by the Henderson-Hasselbach equation (it was originally derived to describe the pH changes resulting from the addition of H^+ or OH^- ions to any buffer system). At a certain concentration of hydrogen ion ($log10^-_1$ [-pH]) specified for each drug, the concentration of LA in its basic form in a solution is equal to the

Structural groups of some commonly used local anesthetics (duration of action)
Amides
Bupivacaine (2–8 h)
Cinchocaine (2–3 h)
Etidocaine (2–6 h)
Levobupivacaine (2–8 h)
Lidocaine (1–2 h)
Mepivacaine (1.5–3 h)
Prilocaine (1–2 h)
Ropivacaine (4–6 h)
Ester of benzoic acid
Cocaine
Esters of meta-aminobenzoic acid
Proxymetacaine
Esters of para-aminobenzoic acid
Benzocaine
Chloroprocaine
Oxybuprocaine
Procaine (30–45 min)
Propoxycaine
Tetracaine

Table 2.
Groups of LA.

concentration of loaded cation. The logarithm of this concentration of hydrogen ion is called pKa.

$$pH = pKa + \log [HCO_3^-]/[H_2CO_3]$$

$$pKa = pH - \log [base]/[conjugate\ acid]$$

$$[base]/[conjugate\ acid] = 1.0$$

The dissociation constant of LA (pKa value) is the highly significant fact affecting the quickness of their beginning of action. The pKa values rule the ratio of the LA that is present in nonprotonated pattern at physiological pH values and hence disposable to spread through tissue walls to its spot of action.

Lower pKa values are conjoint with a prompt beginning of blockade, then more of the drug is present as the unprotonated base at pH 7.4. In contradistinction, bigger values are conjointed with a slower beginning, since fewer of the drug is present as the nonprotonated base at pH 7.4. For instance, lidocaine has a pKa value roughly 7.7. At pH 7.4, around one-third of these drugs is present in solution as the nonprotonated base B and is disposable to spread through the nerve scabbard. In contradistinction, bupivacaine and ropivacaine have a pKa value of 8.1, and at a pH 7.4 only 17% is present in solution as nonprotonated, diffusible base. These discrepancies are responsible for the more prompt beginning of action of lidocaine and slower beginning of action of ropivacaine and bupivacaine.

3.2 Alkalization of local anesthetics

Factors that increase the conversion of the free LA base (B) to the active form (BH^+) in the neuroplasm increase the diffusion gradient and the concentration of BH^+ in the Na^+ channel. This technique is of clinical interest because it is used to shorten the latency of onset of effective anesthesia, particularly useful in the context of extending an epidural block for urgent operative delivery.

The addition of bicarbonate will raise the pH of the weakly acidic solution nearer the pKa. Example: addition of 1.0 mL $NaHCO_3$ 8.4% to 10.0 mL of lidocaine 2% will raise its pH from 6.5 to 7.2; this means more drug will exist in the non-ionized form, so penetration will be more rapid [7].

Carbonation is a variation on alkalization, and is based on a similar principle but with a different site of action; when carbon dioxide diffuses across the neurilemma, it is rapidly buffered by intracellular proteins, so that changes in pH are minimal. Carbonated solutions are unstable, the LA may be precipitated and any added vasoconstrictor is more easily hydrolyzed [8].

3.3 Chirality

Chirality is derived from Greek, and means "having handedness," and is defined a particular type of stereoisomerism. Right and left hands are mirror images of each other but cannot be superimposed when the palms are facing in the same direction (**Figure 4**) [9]. These particular isomers are known as enantiomers and this form of stereoisomerism is dependent on the presence of one or more chiral centers, which typically comprise a carbon atom with four groups attached. These enantiomers have the capacity to rotate polarized light, and, so, are also known as optical isomers.

Enantiomers that rotate polarized light to the right are described as (+), and are the same as dextro or D isomers. Enantiomers that rotate polarized light to the left are described as (−), and are the same as levo or L isomers. The currently accepted

convention is that which assigns a sequence of priority to the four atoms or group attached to the chiral center. The molecule is described as though it were being viewed from the front with the smallest group extending away from the viewer. If the arrangement of the largest to the smallest groups is clockwise, the enantiomer is designated "R" for rectus. If the arrangement is anticlockwise it is designated "S" for sinister. The optical direction is the added to complete the description. Most synthetic chiral drugs are racemic mixtures, less potent because the D-forms are much less active. The clinical behavior of the enantiomers, and in particular their toxicity, is related to the chiral form [10] (**Figure 5** and **Table 3**).

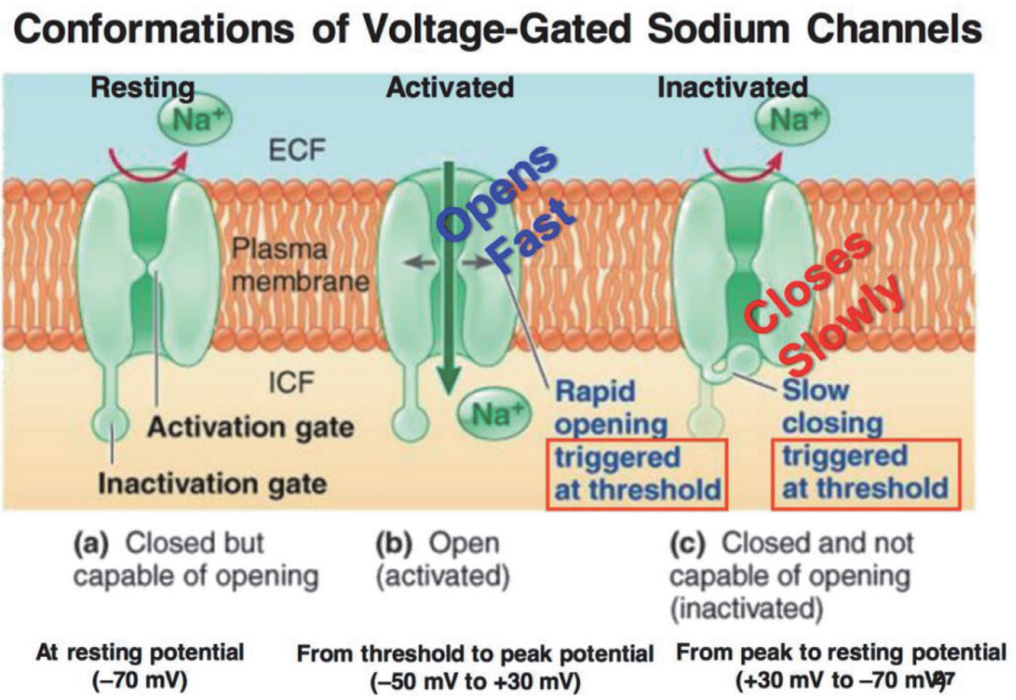

Figure 4.
Na receptor. Memorang.

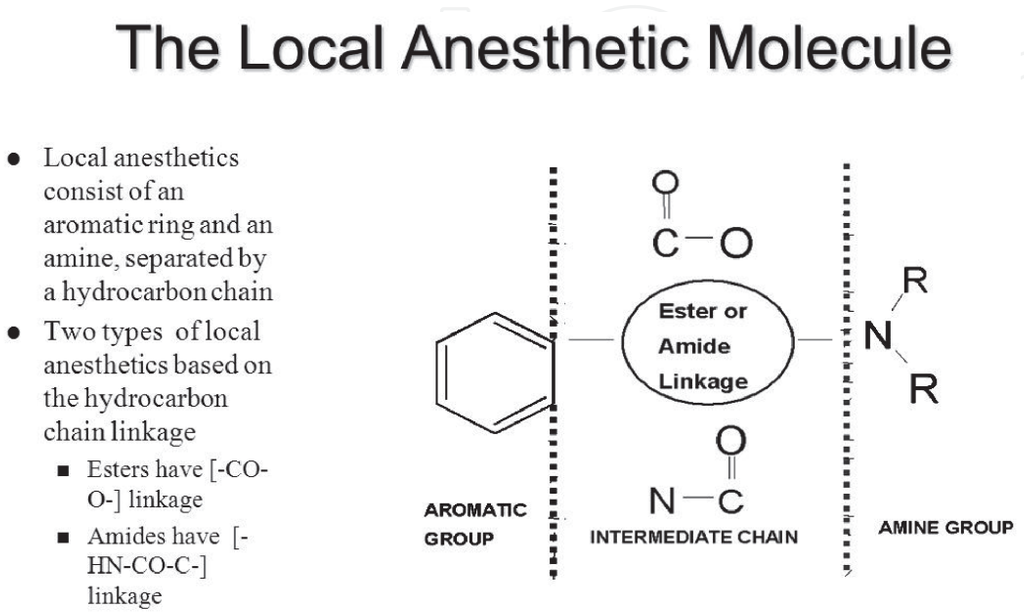

Figure 5.
LA molecule free Google.

Bupivacaine: S(−) enantiomer has less affinity for, and dissociates quicker from myocardial Na^+ channels. The cardio and central nervous system toxicity is reduced. S(−) exerts some vasoconstrictor activity.
Ropivacaine: S(−) enantiomer is a safer cardiovascular profile.
Prilocaine: S(+) enantiomer is a stronger vasoconstrictor, metabolized slowly than the R(−) form which therefore produces higher concentrations of 0-toluidine and a greater risk of methaemoglobinaemia.
Lidocaine: Achiral.

Table 3.
Quimical structure.

4. Pharmacodynamics

Most LA drugs are tertiary amine bases (B), which are dispensed as hydrochloride salts (B.HCL). In this way, their easily disband to pattern acidic solutions:

$$B.HCL < > BH^+ + CL^-$$

After infiltrating the tissues, a ratio of the protonated basic pattern (BH^+) is turned to the unprotonated basic pattern (B) at the pH of the extracellular fluid:

$$BH^+ + HCO_3^- < > B + H_2O + CO_2$$

Solely the unprotonated pattern B penetrates through the neurilemmal membrane, captures H^+ in the neuroplasm, and raises approach to its spot of action in the open Na^+ channel, inducing its blockade. The unprotonated pattern B may further straight permeate to the Na^+ channel across the neurilemma, and recruits H^+ into the Na^+ channel.

It is able to induce blockade by membrane expansion (ME), bring about puffiness of the lipoprotein matrix of the Na^+ channel (e.g., benzocaine). Tetrodotoxin and saxitoxin directly block the Na^+ channel from the exterior of the membrane, close to the external pore [11–13] (**Figure 6**).

The primary target of LAs is the voltage-gated Na^+ channel, which is responsible for the generation of action potentials in excitable membranes, there is an inverse relationship between action potentials and local anesthesia [13]. LAs also interact with many other types of ion channels, particularly K^+ and Ca^{2+} channels, notwithstanding they have a limited relationship at these sites. They do not mostly alter the neuronal resting potential, save in exceedingly raised concentrations. In the same way, they do not change the sill potential needed for impulse spread, even if the gear of depolarization and repolarization is diminished, and conduction velocity is reduced and may cause undesirable side effects, usually considered that the toxic effects of bupivacaine on the heart are partially related to its effects on K^+ and Ca^{2+} channels.

Mammalian voltage-gated Na^+ channels exist in different isoforms in various excitable tissues such as skeletal muscles, cardiac tissues, central nervous system (CNS), and peripheral nervous system (PNS) [14]. In addition, multiple major isoforms are present in CNS and PNS, some of these neuronal Na^+ channels are sensitive to tetrodotoxin (TTX) and some are resistant. Tetrodotoxin (TTX) is a potent naturally occurring neurotoxin isolated from puffer fish; it has been responsible for human intoxications and fatalities. Its usual route of toxicity is via the ingestion of contaminated puffer fish, which are a culinary delicacy, especially in

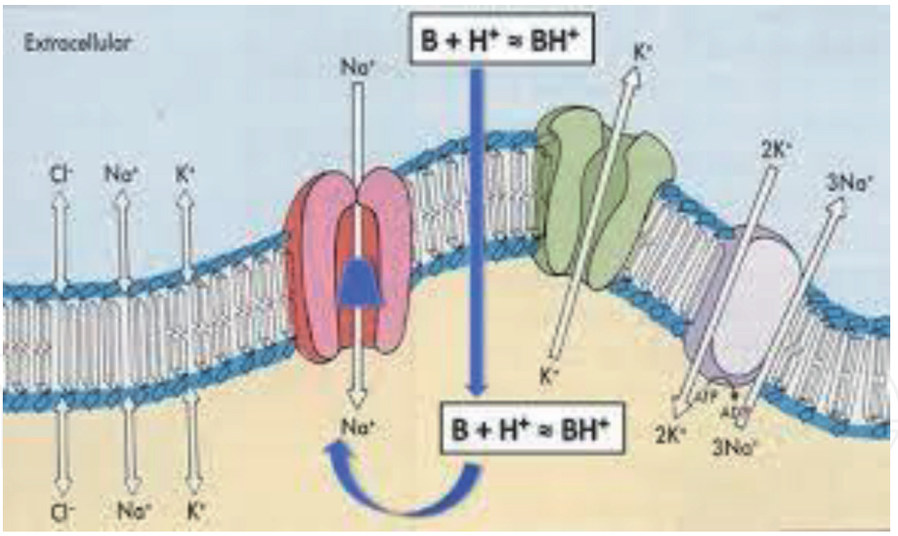

Figure 6.
Amino-base free Google.

Japan. TTX has been an invaluable tool for the identification of various neuronal Na^+ channel isoforms [11–13].

The concentration of LA in blood is determined by the amount injected, the rate of absorption from the injection site, the rate of distribution by tissues, the rate of biotransformation and drug elimination [14]. The patient's factors, such as age, cardiovascular situation, and hepatic function, influence the physiological disposition and the plasma concentration resulting from the LA injected [14, 15].

4.1 Mode and site of action of local anesthetics in Na^+ channels

Mammalian voltage-gated Na^+ channels are normally activated at a threshold of around −50 mV, and the probability of channels being open is maximal around +20 mV. At a single-channel level, the time course of Na^+ channel activation is strongly voltage dependent. The probability of being open during depolarization rises slowly at the threshold and becomes rather fast at the more positive potentials. In contrast, the open Na^+ channels inactivate rapidly, with a dwell time that is generally 1 ms or less. Unlike the activation process, the time course of inactivation of the open Na^+ channel is not voltage dependent [16]. At the level of macroscopic currents, Na^+ currents rise (activate) and decay (inactivate) with overlapping time course, as would be expected from an ensemble of currents from single channels [17, 18].

Detailed kinetic analyses of macroscopic Na^+ currents in the presence of various LAs reveal complicated pharmacological profiles under voltage-clamp conditions. Voltage-sensitive Na^+ channels are integral proteins that cross neuronal membranes and surround an aqueous pore. Most Na^+ channels consist of three subunits (α1, β1, and β2), the largest subunit being α1, the site of ion conduction and LAs binding; the external surface of the α-subunit is heavily glycosylated, which serves to orient the channel properly within the plasma membrane. The α1 unit bears a molecular weight up of 260 kDa, and consists of an unique long peptide chain holding four hydrophobic regions (domains I–IV), which go across the membrane and symmetrically encircle the pore. The four domains are joined to each other by intracellular bridgeworks.

Every domain includes six membrane-spanning somites (S1–S6). The S4 somite is a potential sensor, and the brief curl among S5 and S6 forms portion of the sheathing of the external pore of the gutter. The intracellular bridgework among

two of the domains (III and IV) is the speedy inactivation gateway. This gateway is liable for the speedy inactivation of Na^+ channels.

LAs reduce peak Na^+ currents during the test potential a few minutes after external perfusion of the drug solution at the holding potential (<-100 mV). This reduction in peak current is dose dependent, and the potency ranking of various LAs derived from their dose-response curves correlates well with the relative duration of local anesthesia they elicit in vivo. This LA block of the Na^+ channel at resting potential is termed "tonic block."

Most LAs are found to shift the apparent steady-state inactivation curve to the hyperpolarizing direction. Steady-state inactivation measures the availability of resting Na^+ channels at various prepulse voltages at which Na^+ channels normally do not open [7]. This closed-channel inactivation is strongly voltage dependent, unlike the open channel inactivation. A shift of the steady-state inactivation curve by LA toward the hyperpolarizing direction has significant physiological consequences. To begin with, if the steady-state inactivation curve is indeed shifted by LAs upon binding, a large fraction of Na^+ channels with LAs bound will be in their inactivated state at the resting potential and therefore will be unavailable to carry currents for the generation of action potentials. Another implication is that the inactivated state of the Na^+ channel binds more strongly than other channel states (generalized modulated receptor hypothesis envisioned by Hondeghem and Katzung [19]). They proposed that different states of Na^+ channels (open, resting, and inactivated) have different binding affinities for LAs, and that the affinity of the inactivated state is the highest.

Repetitive pulses produce an additional block of Na^+ currents in the presence of LA. This additional block of Na^+ currents is termed "use-dependent block" or "frequency-dependent block," with the two terms used interchangeably. The use-dependent block by LAs may be physiologically important for pain therapy, as many afferent fibers fire action potentials at a high frequency, particularly in the pathological states. In theory, LAs with a potent use-dependent attribute will be more effective than LAs without this attribute in blocking the high-frequency abnormal firings of sensory afferent fibers.

4.2 Potency of local anesthetic

The potency of a LA is regulated mainly by lipid solubility, the time of onset by the pKa of the substance, and the duration of action by protein binding. The more lipophilic the LA, the more potent it is [20, 21]. Nerve-blocking potency of LAs increases also with increasing molecular weight [22].

LA appears to have a ceiling effect. Above a partition coefficient of 4 there is no observed increase in potency [23]. Unfortunately, greater lipid solubility also increases toxicity, decreasing the therapeutic index for more hydrophobic drugs. Larger more lipophilic LAs permeate nerve membrane more readily and bind Na^+ channels with greater affinity (**Table 4**).

More lipid-soluble LAs are relatively water insoluble, high protein bound in blood, and less readily removed by bloodstream from nerve membranes, and this affinity of the drug to lipid membranes and therefore greater proximity to its site of action in the Na^+ channel.

4.3 Onset and duration of action of local anesthetics

The onset of nerve conduction blockade depends on the physicochemical properties of each LA. The latency also depends on the dose or concentration of the drug used. The duration of the effect of local anesthetics is very variable (**Table 5**).

Local anesthetic	Partition coefficient
Benzocaine	1.44
Procaine	2.51
Mepivacaine	2.69
Prilocaine	2.73
Lidocaine	3.40
Bupivacaine	4.05
Etidocaine	4.19
Tetracaine	4.32
Oxybuprocaine	4.38

Table 4.
Partition coefficients (n-octanol/water) of some local anesthetics.

Short effect	Procaine
	Cloroprocaine
Moderate effect	Lidocaine
	Mepivacaine
	Prilocaine
Long effect	Tetracaine
	Bupivacaine
	Ropivacaine
	Etidocaine

Table 5.
Onset and duration.

The peripheral vascular effects of the local anesthetic have significant effects; many anesthetics have a biphasic effect on vascular smooth muscle, at low concentrations they produce vasoconstriction and at higher concentrations they produce vasodilation. However, the vasodilator effect differs between the different drugs, the effects on vascular blood flow and its tone are complex, and vary among other factors, depending on the concentration, time, and vascular bed near the point of application.

5. Pharmacokinetics

Pharmacokinetics was originally described as the quantitative studio and mathematical review of drug and it's metabolite in the organism. The concept has been mostly obsequious to the prosecution of drug absorption, distribution, metabolism and excretion, and to their explanation in numerical terminus. Pharmacokinetics is once in a while portrayed as "what the body does to drugs." The two highly large pharmacokinetic uniforms are:

- Volume of distribution (V)
- Clearance (CL)

The volume of distribution depicts the seeming volume disposable in the organism for the allocation of the drug, whereas the clearance shows capacity of the organism to eliminate the drug. These two uniforms are kindred to the terminal or elimination half-life of the drug. In other words, after one half-life, the concentration of the drug in the body will be half of the starting dose. Half-life is defined as the time required for the plasma concentration to decrease by 50% during the terminal phase of decline, by the following expression:

$$t½ = 0.693 \times Vd/CL.$$

Accordingly, the terminal half-life is regularly heterogeneous, which depends on the early pharmacokinetics constant volume (V) and clearance (CL). A prolonged terminal half-life can throw back an enhanced volume of distribution, a narrow clearance, or together these changes, while a brief terminal half-life can reflect a decreased volume of distribution, an enhanced clearance or both together [8] (**Table 6**).

Clearance depicts the quantity of blood or plasma since that a drug would need to be thoroughly eliminated in unit time in order to guarantee its put-out from the body. It is a theoretic thought, inasmuch as in practice drugs are incompletely withdrawn from a nay larger quantity of plasma. Clearance values are generally expressed as a quantity cleared in unit time and are generally measured in mL min^{-1} or L h^{-1}.

Also, clearance can be determined as the timing of drug elimination (mg min^{-1}) per unit of blood or plasma concentration (mg mL^{-1}).

$$\text{plasma clearance } \left(\text{mL min}^{-1}\right) = \frac{\text{timing of drug removal } \left(\text{mg min}^{-1}\right)}{\text{plasma centralization } \left(\text{mg mL}^{-1}\right)}$$

Plasma clearance is as a rule steadfast; the cadence of drug removal is right away proportional to plasma concentration. Total body clearance is the addition of various ways of drug elimination that are carried out by various organs in the body:

$$CL = CL_R + CL_H + CL_X$$

where CL is total clearance, CL_R is renal clearance, CL_H is hepatic clearance and CL_X is clearance by other routes (**Table 7**).

After absorption from the site of injection, the plasma concentration of LAs depends on their rate of distribution in tissues and their elimination from the body. Subsequent to an intravenous injection, the plasma concentration of all LAs in general falls in a biexponential ways. There is an incipient quick allocation time (half-life 1–3 min), conjoint with their rapid inlet by greatly perfused organs (e.g., lung, liver, kidney). Afterward, there is a slower reduction in plasma centralization, which depicts the put-out of LAs by metabolism and excretion. The final half-life of most ester anesthetics is comparatively brief (10 min) owing to their prompt

Drug	Volume of distribution (ml/kg)	Volume of distribution (L 70 kg)
Lidocaine	900 (500–1300)	63 (35–91)
Bupivacaine	1050 (650–1450)	74 (46–104)
Prilocaine	2700 (2100–3300)	189 (147–241)

Table 6.
Volume of distribution.

Drug	Hepatic clearance (mL min^{-1} kg^{-1})	Hepatic clearance (mL min^{-1} 70 kg^{-1})
Lidocaine	17.0 (12.6–21.4)	1190 (882–1498)

Table 7.
Hepatic clearance.

	Terminal half-life (min)	Clearance (mL min^{-1} kg^{-1})	Apparent volume of distribution	Metabolites (L kg^{-1})
Cocaine	48	31	2.0	Norcocaine
				Ecgonine
				Benzoylated
Procaine	8	60	0.7	Diethylaminoethanol
				p-aminobenzoate
Tetracaine	15	47	1.0	Butyl-aminobenzoate
				Dimethyl-aminoethanol
Lidocaine	100	15	1.3	Monoethylglycine-
				xylidide
				Ethylglycine
				2,6-xylidine
				4-hydroxy-2,6-xylidine
Prilocaine	100	34	2.7	N-propylamine
				o-toluidine
Bupivacaine	200	9	1.1	Pipecolic acid
				Pipecolyl-xylidide
Levobupivacaine	200	9	1.1	Pipecolic acid
				Pipecolyl-xylidide
Ropivacaine	110	7	0.7	3-Hydroxy-ropivacain
				4-Hydroxy-ropivacain

Table 8.
Pharmacokinetics and metabolism of local anesthetics.

hydrolysis by plasma cholinesterase, in hallmark, the terminal half-life of the amides oscillates from 100 min (lidocaine) to 200 min (bupivacaine).

Their volume of distribution is rather greater than total body water, while their plasma clearance is usually less than liver blood flow (**Table 8**).

Some clinical conditions can modify the pharmacokinetics of LAs, specially cardiovascular disorders and chronic hepatic diseases like cirrhosis can decline the clearance and volume of distribution of LAs, with changeable impact on the terminal half-life. In neonates, the clearance of LAs is diminished and their half-life is sustained.

6. Conclusions

LAs are drugs widely used in medicine and dentistry. These medications cause reversible neural block by their action in the sodium channels (**Figure 7**) located in

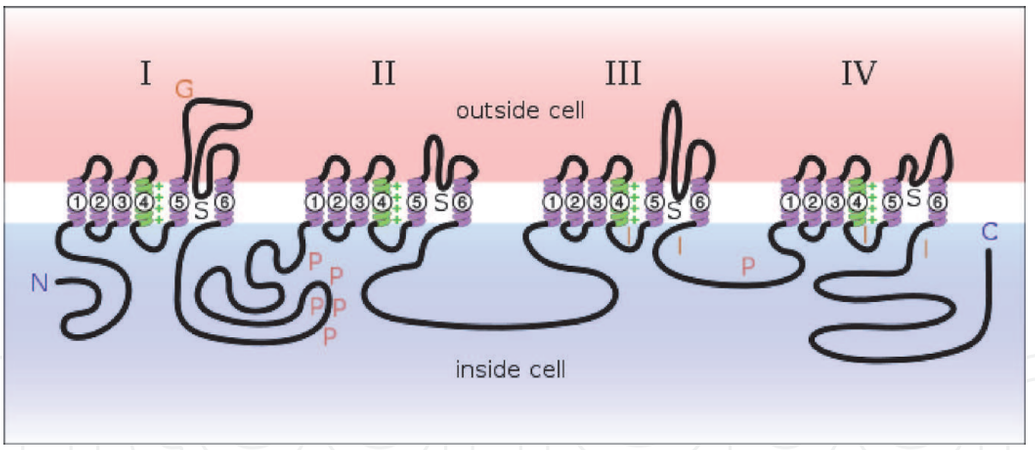

Figure 7.
Sodium channel. Wikipedia.

the nerve membranes. The unprotonated molecule configuration of the LA is introduced through the membrane from the outside and the protonated molecule acts with the sodium channel from the inside. The potency of a LA is given by liposolubility, the onset time by dissociation constant (pKa), and the duration of action by protein binding. Local anesthetics are weak bases whose structure consists of an aromatic moiety connected to a substituted amine through an ester or amide linkage. Consequently, LAs are classified as aminoester or aminoamide compounds. Amino acids are hydrolyzed by plasma cholinesterase, while aminoamides are metabolized in the liver. Aminoamides cause less allergic reactions.

Conflict of interest

The author declares no conflict of interests.

Author details

Javier Marcos Michel-Levy
Hospital Obrero N°8, Caja Nacional de Salud, Trinidad-Beni, Bolivia

*Address all correspondence to: jmichel_levy@hotmail.com

References

[1] Brunton L, editor. Goodman and Gilman. The Pharmacological Bases of Therapeutics. 12th ed. New York: McGraw Hill; 2011

[2] Goldin AL, Barchi RL, Caldwell JH, Hofmann F, Howe JR, Hunter JC, et al. Nomenclature of voltage-gated sodium channels. Neuron. 2000;**28**(2):365-368. DOI: 10.1016/s0896-6273(00)00116-1

[3] Hadzic A. Hadzic's Textbook of Regional Anesthesia and Acute Pain Management. The New York School of Regional Anesthesia. 2nd ed. NY: McGraw-Hill Education; 2017

[4] Bovill J, Fee H. Physiology for Anaesthesiologists. UK: Taylor and Francis Group; 2004

[5] Becker DE, Reed KL. Essentials of local anesthetic pharmacology. Anesthesia Progress. 2006;**53**(3):98-109. DOI: 10.2344/0003-3006(2006)53[98, EOLAP]2.0.CO;2

[6] Gropper MA, editor. Miller's Anesthesia. 9th ed. US: Elsevier; 2019

[7] Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. 1952. Bulletin of Mathematical Biology. 1990;**52**(1–2):25-71. DOI: 10.1007/bf02459568

[8] Calvey N, Williams N. Principles and Practice of Pharmacology for Anaesthetists. 5th ed. New Jersey: Wiley, John & Sons, Inc.; 2008

[9] Carrada PS. Carta al editor. Anestesia en México. 2006;**18**(2):181-182

[10] Weiskopf R, Nau C, Strichartz G. Drug chirality in anesthesia. Anesthesiology. 2002;**97**:497-502

[11] Lorentz MN, Stokes AN, Rößler DC, Lötters S. Tetrodotoxin. Current Biology. 2016;**26**(19):R870-R872. DOI: 10.1016/j.cub.2016.05.067

[12] Bane V, Lehane M, Dikshit M, O'Riordan A, Furey A. Tetrodotoxin: Chemistry, toxicity, source, distribution and detection. Toxins (Basel). 2014;**6**(2):693-755. DOI: 10.3390/toxins6020693

[13] Thottumkara AP, Parsons WH, Du Bois J. Saxitoxin. Angewandte Chemie (International Ed. in English). 2014;**53**(23):5760-5784. DOI: 10.1002/anie.201308235

[14] Tucker GT. Pharmacokinetics of local anaesthetics. British Journal of Anaesthesia. 1986;**58**(7):717-731. DOI: 10.1093/bja/58.7.717

[15] Rosenberg PH, Veering BT, Urmey WF. Maximum recommended doses of local anesthetics: A multifactorial concept. Regional Anesthesia and Pain Medicine. 2004;**29**(6):564-575. DOI: 10.1016/j.rapm.2004.08.003

[16] Skou JC. Local anaesthetics. VI. Relation between blocking potency and penetration of a monomolecular layer of lipoids from nerves. Acta Pharmacologica et Toxicologica (Copenh). 1954;**10**(4):325-337. DOI: 10.1111/j.1600-0773.1954.tb01349.x

[17] Aldrich RW, Corey DP, Stevens CF. A reinterpretation of mammalian sodium channel gating based on single channel recording. Nature. 1983;**306**(5942):436-441. DOI: 10.1038/306436a0

[18] Hille B. Gating mechanisms. In: Ionic Channels of Excitable Membranes. Sunderland, Massachusetts: Sinauer; 1992. pp. 472-503

[19] Hondeghem LM, Katzung BG. Time- and voltage-dependent

interactions of antiarrhythmic drugs with cardiac sodium channels. Biochimica et Biophysica Acta. 1977;**472** (3–4):373-398. DOI: 10.1016/0304-4157 (77)90003-x

[20] Grouls RJ, Ackerman EW, Korsten HH, Hellebrekers LJ, Breimer DD. Partition coefficients (n-octanol/water) of N-butyl-p-aminobenzoate and other local anesthetics measured by reversed-phase high-performance liquid chromatography. Journal of Chromatography. B, Biomedical Sciences and Applications. 1997;**694**(2): 421-425. DOI: 10.1016/s0378-4347(97) 00207-7

[21] Dullenkopf A, Borgeat A. Local anesthetics. Differences and similarities in the "-cains". Anaesthesist. 2003; **52**(4):329-340. DOI: 10.1007/ s00101-003-0463-5

[22] Sanchez V, Arthur GR, Strichartz GR. Fundamental properties of local anesthetics. I. The dependence of lidocaine's ionization and octanol: buffer partitioning on solvent and temperature. Anesthesia and Analgesia. 1987;**66**(2):159-165

[23] Bricker S. The Anaesthesia Science Viva Book. 3rd ed. New York, NY: Cambridge University Press; 2017