Local Anesthetics and Additives: Options and Misconceptions

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General Considerations

Regional anesthesia began in 1884 when Köller and Gartner performed topical cocaine anesthesia of the eye.[1-4] Later in 1884 Halsted performed mandibular nerve and brachial plexus blocks.[1-3] Spinal and epidural anesthesia, local anesthetic (LA) additives, and less-toxic, synthetic LAs were soon introduced.[2-4] This review will consider LA mechanisms, pharmacodynamics, toxicity, and how additives can enhance local and regional anesthesia.

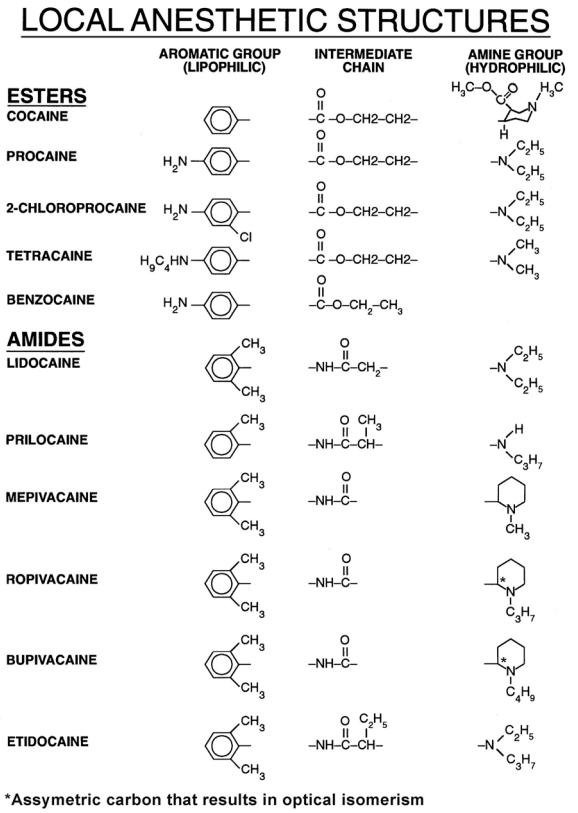

Figure 1.

LA Chemistry and Chirality

LAs contain an aromatic ring and an amine, separated by a hydrocarbon chain (Figure 1).[2,3,5,6] The two families of LAs, esters and amides, are defined by the chemical link between the aromatic moiety and the hydrocarbon chain. Ropivacaine and levobupivacaine exist as single (S-) enantiomers. Other LAs either exist as racemates or have no asymmetric carbons.

Electrophysiology of Na Channels and LAs

LAs bind voltage-gated Na channels to inhibit nerve conduction. Na channels contain 1 larger α-subunit and 1 or 2 smaller β-subunits. The α-subunit, the site of ion conduction and LA binding, has 4 homologous domains each having 6 α-helical, membrane-spanning segments.[7,8] Humans have 10 Na channel genes on 4 chromosomes. Specific genes contribute Na channel forms to each of unmyelinated axons, nodes of Ranvier, and small dorsal root ganglion nociceptors.[9] Na channels exists in at least 3 native conformations: "resting," "open," and "inactivated".[10] During an action potential, neuronal Na channels "open" briefly, allowing extracellular Na ions to flow into the cell, depolarizing the plasma membrane. After only a few milliseconds, Na channels "inactivate" (whereupon the Na current ceases). Na channels return to the "resting" conformation with membrane repolarization. In mammalian myelinated fibers, membrane repolarization requires no contribution from K currents.[5,10] Channels are likely "gated" by paddle-shaped voltage sensors nested in the plasma membrane.[11,12]

Local anesthesia results when LAs bind Na channels and inhibit the Na permeability that underlies action potentials in peripheral neurons.[5,10] LA binding has been localized to the D4 S6 region of the α-subunit.[13] LA inhibition of Na currents increases with repetitive depolarizations, often called "use-dependent" block.[5,10] Repetitive trains of depolarizations increase the likelihood that a LA will encounter a Na channel that is "open" or "inactivated," both of which forms have greater LA affinity than "resting" channels.[5,10,14] Aside from LAs, many compounds inhibit Na channels: general anesthetics, α_2 agonists, tricyclic antidepressants, and nerve toxins.[5,15-17]

LA Pharmacodynamics

Maximum doses

It is illogical to speak of one, universal, maximal "safe" dose of LA.[18] The maximal tolerable dose depends on many factors, including the site and timing of administration, the presence or absence of clonidine or epinephrine, patient size and body habitus, pregnancy, and the presence of disease. For example, with the same LA dose, intercostal blocks consistently produce greater peak LA concentrations than plexus or epidural blocks.[3,6,19]

LA Potency and Duration

Nerve-blocking potency of LAs increases with increasing molecular weight and increasing lipid solubility.[20,21] Larger, more lipid-soluble LAs are relatively water-insoluble, highly protein-bound in blood, less readily "washed out" from nerves, and bind Na channels with greater affinity. Increased lipid solubility associates with increased protein binding, increased potency, longer duration of action, and an increased tendency for severe cardiac toxicity. Extent and duration of anesthesia can be correlated with LA content of nerves in animal experiments.[22-24]

LA Speed of Onset

In general, the onset of anesthesia slows with increasing LA lipid solubility. At any pH, the percentage of LA molecules present in the uncharged, more-membrane-permeable form decreases with increasing pKa.[19-21] However, two of the "fastest" LAs, etidocaine (highly lipid soluble) and chloroprocaine (high pKa) illustrate the foolishness of generalizations about physical-chemical properties and LA speed of onset.

Differential Sensory Nerve Block

A LA nerve block sufficient to block incisional pain, will usually also impair motor function.[2,3,5] LAs will block smaller fibers at lower concentrations than are required to block larger fibers of the same type.[25] Bupivacaine and ropivacaine (vs. mepivacaine) are relatively selective for sensory fibers.[26] Specific Na channel gene products are found in unmyelinated nerves, motor nerves, and dorsal root ganglia, offering the tantalizing possibility that specific antagonists may some day be produced for these specific Na channel forms.[27,28]

Other Factors Influencing LA Activity

Many factors influence the quality of regional anesthesia, including the LA dose, site of administration, temperature, pregnancy, and additives. As the LA dose increases, the likelihood of success and the duration of anesthesia increase, while the delay of onset and tendency for differential block decrease. In general, the fastest onset and shortest duration of anesthesia occur with spinal or subcutaneous injections; a slower onset and longer duration are obtained with plexus blocks.[19] Spread of neuraxial anesthesia increases during pregnancy due to decreases in thoraco-lumbar CSF volume and an increased neural susceptibility to LAs.[29,30]

LA Additives

Currently popular LA additives include α_1- and α_2-adrenergic agonists, opioids, ketorolac, sodium bicarbonate, and hyaluronidase. These are variously added to increase the safety, quality, intensity, duration, and rate of onset of anesthesia, and to reduce blood loss.[6] Some additive effects are common to most blocks: epinephrine is added to constrict vessels and to serve as a marker for intravascular injection[3]; α_2-adrenergic agonists have LA properties and alter LA pharmacodynamics;[17] sodium bicarbonate increases the fraction of LA molecules that are uncharged, increases the apparent LA potency, and speeds the onset of some nerve blocks.[3,6,31] Other additive effects are specific to the particular form of regional anesthesia. Use of additives in obstetric anesthesia is beyond the scope of this review. Typical uses of additives are tabulated below:

Additives for specific blocks

Local infiltration: Epinephrine prolongs duration and reduces blood concentrations of LAs; it also reduces bleeding .[32] The pain of local infiltration can be reduced by addition of sodium bicarbonate.[33]

Superficial cervical plexus blocks: Epinephrine reduces peak bupivacaine concentrations in blood.[34,35] Clonidine-bupivacaine was associated with a slower heart rate compared to epinephrine-bupivacaine, but there was no heart rate difference comparing epinephrine-bupivacaine to plain bupivacaine.

Ophthalmic blocks: Hyaluronidase improves reliability and rate of onset of anesthesia. Epinephrine, bicarbonate and clonidine also improve anesthesia.[36,37]

Intravenous regional anesthesia: Clonidine and dexmedetomidine reduce intraoperative and postoperative discomfort with IVRA.[38] Ketorolac improves intraoperative anesthesia and postoperative analgesia.[39]

Minor peripheral blocks: LA solutions containing epinephrine have been used for digital nerve blocks without ischemic sequelae.[40]

Brachial plexus blocks: Epinephrine reduces blood LA concentrations and serves as a marker for IV injection.[41] Clonidine improves anesthesia from lidocaine and mepivacaine, but has no major effect on bupivacaine or ropivacaine.[41] Bicarbonate reduces the latency of anesthesia and complete paralysis, particularly with epinephrine-containing LA solutions.[41]

Intercostal blocks: Epinephrine is nearly always used to decrease blood LA concentrations.[42]

Epidural and caudal anesthesia and analgesia: Epidural epinephrine reduces blood LA concentrations and increases cardiac output.[3,6,43] Epidural clonidine produces analgesia, sedation, and increased LA blood concentrations.[44-46] Epidural combinations of LAs and opioids provide superior analgesia to the agents given separately.[47] When combined with bupivacaine, nausea, vomiting, and urinary retention were more likely with morphine than with fentanyl or meperidine; pruritus was more common with morphine and diamorphine than with methadone or meperidine.[48]

Spinal anesthesia and analgesia: Dextrose and water influence baricity, distribution of LAs within the CSF, and dermatomal spread of spinal anesthesia (SPA).[49] Vasoconstrictors prolong tetracaine SPA with less effect on lidocaine.[50,51] Analgesia from isobaric LA solutions is prolonged by addition of both α_1 and α_2 agonists.[52] Clonidine (intrathecal or oral) may be used to prolong spinal anesthesia.[53] Adding fentanyl to LA solutions improves the quality of intraoperative and postoperative SPA without prolonging motor block, time to voiding, or recovery time.[54]

LA Blood Concentrations, Protein Binding, Metabolism, and Pharmacokinetics

In blood, all LAs are partially protein-bound, primarily to α_1-acid glycoprotein (AGP) and secondarily to albumin.[2,3,6] Affinity for AGP increases with LA hydrophobicity and decreases with protonation.[55] Extent of protein binding is influenced by the concentration of AGP. Both protein binding and protein concentration decline during pregnancy.[56] During longer-term infusion of LA and LA-opioid combinations concentrations of serum binding proteins progressively increase.[57] There is considerable first-pass uptake of LAs by lung.[58]

Esters undergo rapid hydrolysis in blood, catalyzed by pseudocholinesterase.[2,3,6] Procaine and benzocaine are metabolized to para-aminobenzoic acid (PABA).[3] The amides undergo oxidative *N*-de-alkylation in the liver (by various forms of cytochrome P450).[2,3,6] Prilocaine is metabolized to *o*-toluidine, a cause of methemoglobinemia.[3] Amide LA clearance is highly dependent on hepatic blood flow, hepatic extraction, and enzyme function, and is reduced by factors which decrease hepatic blood flow, such as β-adrenergic receptor or H_2-receptor blockers, and by heart or liver failure.[2,3,6]

Toxic Side Effects of LAs

Aside from Na channels, LAs will inhibit many other targets, including voltage-gated K and Ca channels, K_{ATP} channels, enzymes, NMDA receptors, β-adrenergic receptors, G-protein-mediated modulation of K and Ca channels, nicotinic acetylcholine receptors, and phosphorylation of extracellular receptor-activated kinases.[5,59-62] LA binding to these other sites could underlie spinal or epidural analgesia, and could contribute to systemic side effects.

Central Nervous System (CNS) Side Effects

LA CNS toxicity results from inhibition of excitatory pathways in the CNS. Increasing LA doses produce a stereotypical sequence of signs and symptoms culminating in seizures.[2,3,6,19,63] Further LA dosing may produce CNS depression, and respiratory arrest. More potent LAs produce seizures at lower blood concentrations and lower doses. Metabolic and respiratory acidosis decrease the convulsive dose.[64] CNS toxicity can promote CV toxicity.[63]

Cardiovascular (CV) Toxicity

LAs bind and inhibit cardiac Na channels.[2,10] Bupivacaine binds more avidly and longer than lidocaine to cardiac Na channels.[5] Certain R(+) isomers bind cardiac Na channels more avidly than S(-) isomers.[65] This led to the development of levobupivacaine and ropivacaine. LAs inhibit conduction in the heart with the same rank order of potency as for nerve block.[66] LAs produce dose-dependent myocardial depression, possibly from interference with Ca signaling mechanisms within cardiac muscle.[67] In the heart, LAs bind and inhibit Ca and K channels at concentrations greater than those at which binding to Na channels is maximal.[5,10,67] LAs bind β-adrenergic receptors and inhibit epinephrine-stimulated cyclic AMP formation, either of which could underlie the refractoriness of bupivacaine CV toxicity to standard resuscitation with epinephrine.[68,69]

In animals, most LAs will not produce CV toxicity with blood concentration less than 3 times those producing seizures; however, there are clinical reports of simultaneous CNS and CV toxicity with bupivacaine.[2,3,6] In dogs, supraconvulsant doses of bupivacaine more commonly produce arrhythmias than supraconvulsant doses of ropivacaine or lidocaine.[70] LAs produce CV signs of CNS excitation (increased heart rate, arterial blood pressure, and cardiac output) at lower concentrations than those associated with cardiac depression.[63]

In rats, the rank order for cardiac toxicity appears to be bupivacaine > levobupivacaine > ropivacaine.[71-73] In dogs, both programmed electrical stimulation and epinephrine resuscitation elicited more arrhythmias with bupivacaine and levobupivacaine than with lidocaine or ropivacaine.[74-76] When LAs were given to the point of extreme hypotension, dogs receiving lidocaine could be resuscitated, but required continuing infusion of epinephrine to counteract LA-induced myocardial depression. Conversely, many dogs receiving bupivacaine or levobupivacaine to the point of extreme hypotension could not be resuscitated. After bupivacaine, levobupivacaine, or ropivacaine, dogs that could be defibrillated often required no additional therapy.[74-76] Studies in pigs also show that bupivacaine may have a greater propensity than lidocaine for arrhythmogenesis. The ratio of potency (lidocaine: bupivacaine) for myocardial depression was 1:4; whereas that for arrhythmogenesis was 1:16.[77] A common clinical question is whether all LA cardiovascular toxicity arises from the same mechanism. Given that the potent LAs (such as bupivacaine) seem much more prone to arrhythmogenesis than less potent agents (such as lidocaine), it seems likely that the mechanism of cardiovascular toxicity depends on which LA has been administered.

Neurotoxic Effects of LAs

During the 1980s, 2-chloroprocaine (formulated with Na metabisulfite at an acidic pH) occasionally produced cauda equina syndrome after accidental intrathecal injection of large doses.[3,6,78,79] Reports of neurotoxicity virtually disappeared when the compound was reformulated, but have now returned following the introduction of generic products containing the original metabisulfite and pH.[80] Whether the toxin is 2-chloroprocaine or metabisulfite remains unsettled: 2-chloroprocaine is now being tested as a substitute for lidocaine in human spinal anesthesia.[81] At the same time, other investigators have linked neurotoxic reactions to the LA rather than to metabisulfite.[82]

Presently, there is controversy about transient neurologic symptoms and persisting sacral deficits after lidocaine spinal anesthesia. Unlike other spinal LA solutions, lidocaine permanently interrupts conduction when applied to isolated nerves or to isolated neurons, and at equipotent spinal doses is more likely to produce persisting deficits.[83,84]

Treatment of LA Toxicity

Treatment of adverse LA reactions depends on their severity. Minor reactions can be allowed to terminate spontaneously. LA-induced seizures should be managed by maintaining the airway and providing oxygen. Seizures may be terminated with intravenous thiopental (1-2 mg/kg), midazolam (0.05-0.10 mg/kg), or propofol (0.5-1 mg/kg).[3,6] If LA intoxication produces CV depression, hypotension may be treated by infusion of intravenous fluids and vasopressors (phenylephrine 0.5-5 mcg/kg/min, norepinephrine 0.02-0.2 mcg/kg/min, or vasopressin 2-20 units IV). If myocardial failure is present, epinephrine (1-15 mcg/kg IV bolus) may be required. When toxicity progresses to cardiac arrest, the guidelines for Advanced Cardiac Life Support are reasonable;[85] however, a recent survey of academic anesthesia departments illustrated a lack of consensus regarding appropriate resuscitation for LA CV toxicity.[86] I suggest that amiodarone and vasopressin be substituted for lidocaine and epinephrine, respectively.[87-89] With unresponsive bupivacaine cardiac toxicity, intravenous lipid or cardiopulmonary bypass should be considered.[90] Recent animal experiments demonstrate the remarkable ability of lipid infusion to resuscitate animals from bupivacaine over dosage, even after 10 minutes of unsuccessful "conventional" resuscitative efforts.[91-93] A case report provides some evidence that lipid infusion may also be effective in humans.[94]

Summary

After 120 years of medical use, LAs remain versatile and important tools for the physician. Some features of local anesthesia are well understood. Peripheral nerve blocks almost certainly result from LA inhibition of Na channels in neuronal membranes. Conversely, the mechanisms of spinal and epidural anesthesia remain poorly defined. The mechanisms by which LAs produce CV toxicity likely vary: the more potent agents (e.g., bupivacaine) may produce arrhythmias through (likely) a Na channel action, and the less potent agents (e.g., lidocaine) may produce isolated myocardial depression via other pathways.

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