Local Anesthetics: Pharmacology and Clinical Use

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Coca was being used in South American religious rituals when the first Spanish explorers arrived. Scherzer brought coca back to Europe where Niemann purified and characterized cocaine. Cocaine underwent exploratory animal and clinical experimentation, resulting in the 1884 report of topical anesthesia of the cornea by Koller (1,2). Soon thereafter nearly all currently popular local and regional anesthesia techniques had been described.

Cocaine and all local anesthetics (LAs) contain an aromatic ring at one end of the molecule and a tertiary amine at the other, separated by hydrocarbon chain (Fig. 1) (1–4). LAs segregate into esters and amides, based on the chemical link between the aromatic moiety and the hydrocarbon chain. Ropivacaine and levobupivacaine exist as single (S-) optical isomers. Other LAs are prepared as racemates (cocaine, prilocaine, etidocaine, mepivacaine, bupivacaine) or have no asymmetric carbons.

Electrophysiology, Na Channels, and LA Actions

Local anesthesia results when LAs bind sufficient Na channels in a nerve, inhibiting the Na permeability that underlies action potentials and preventing impulse conduction (3,5). Na channels are heavily glycosylated integral membrane proteins containing 1 larger α-subunit and 1 or 2 smaller β-subunits. The α-subunit is the site of ion conduction and LA binding, and has 4 homologous domains (D1-D4) each with 6 α-helical transmembrane segments (S1-6).

During a neuronal action potential, 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" (assume a conformation that does not permit Na^+ current). Mammalian myelinated fibers repolarize (return to resting membrane potential) with little contribution from K currents (3,5).

Na channels can exist in at least three conformations: "resting," "open," and "inactivated." Membrane potential influences Na channel conformations and LA affinity for Na channels. LA binding is favored by depolarizing potentials and by repetitive depolarizations, the latter phenomenon being called "use-dependent" or phasic block (Fig. 2). A good explanation for this is that both "open" (ion-conducting) and "inactivated" channels have greater LA affinity than "resting" channels (nonconducting Na channels that could be activated by a depolarization) (3,5).

LA binding has been genetically mapped to D4-S6, and inactivation to D3-S6 of the Na channel α-subunit (6). LAs will bind to many different sites; thus, the molecular mechanisms by which LAs produce spinal or epidural analgesia may include LA binding to targets other than Na channels. Other chemicals also bind and inhibit Na channels, including tetrodotoxin (and other toxins), calcium channel blockers, α_2-adrenergic agonists, volatile general anesthetics, and meperidine (3,5,7).

General Characteristics of Local Anesthesia

The clinical actions of a LA may be described by its potency, duration of action, speed of onset and tendency for differential block. These properties do not sort independently.

LA Potency

There tends to be an association between a LA's octanol:water partition coefficient and the LA potency in vitro (8,9). The larger, more lipophilic LAs permeate nerve membranes more readily and bind Na channels with greater affinity.

LA Duration: Regulated By Protein Binding?

It is a misconception that duration of local anesthesia directly relates to LA protein binding. Protein binding refers to the mode by which drugs are transported in blood (1,2,4). More lipid-soluble LAs are relatively water-insoluble and, therefore, highly protein-bound. More lipid soluble LAs are less readily removed by the

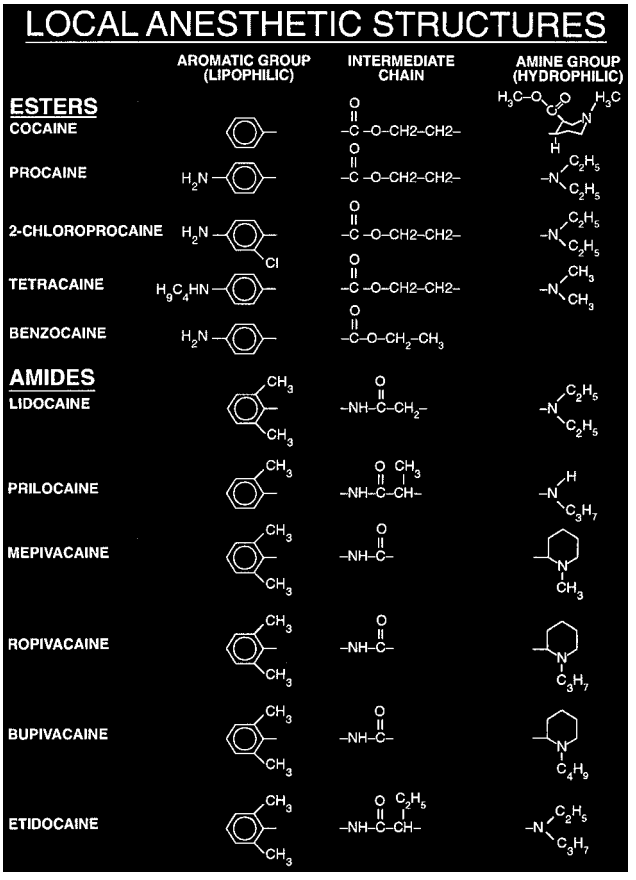

Figure 1. Common local anesthetics.

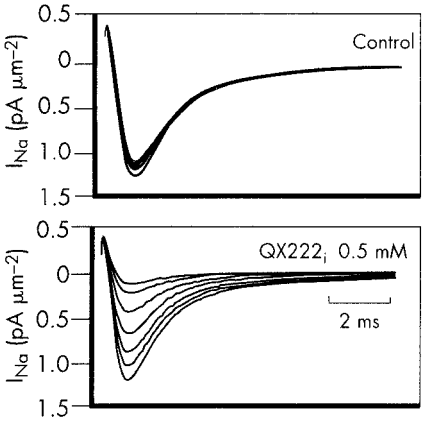

Figure 2. Repetitive pulses produce trains of nearly identical (downward) Na currents in voltage-clamped cardiac membranes under control conditions. After application of the lidocaine derivative QX222, successive pulses produce progressively decreasing Na currents (from J Gen Physiol 1994;103:19–43).

blood stream from nerve membranes, and they are more slowly "washed out" from isolated nerves in vitro. To be sure, long duration of LA action correlates with high lipid solubility, but this also relates, as previously noted, both to increased potency and to increased protein binding in blood.

LA Speed of Onset: Controlled by pKa?

For most LAs, the onset of anesthesia in isolated nerves is associated inversely with both lipid solubility and pK_a. And at any pH, the percentage of LA molecules present in the uncharged form (the more membrane permeable form) decreases with increasing pK_a (8,9). However, of the two LAs of fastest onset in the clinic, etidocaine and chloroprocaine, the former is highly lipid soluble and the latter's pKa is greater than nearly all other LAs.

Differential Sensory Nerve Block

Regional anesthesia sufficient for skin incision usually cannot be obtained without motor impairment (1–3). All LAs will block myelinated or unmyelinated fibers of smaller diameter at lower concentrations than are required to block larger fibers of the same type; thus Aδ pain fibers are more LA-sensitive than Aα motor fibers. Bupivacaine and ropivacaine are relatively selective for sensory fibers: compared to mepivacaine, bupivacaine demonstrates more rapid onset of sensory than motor block whereas mepivacaine blocks sensory and motor nerves at the same rate (10). Adequate sensory analgesia, with little or no motor block, can be achieved for postoperative and labor pain, particularly when the LA is combined with opioids and/or α_2 agonists.

Other Factors Influencing LA Activity

A variety of factors influence the quality of regional anesthesia, including the LA dose, site of administration, additives, and pregnancy. As the LA dose increases, both the likelihood of success and the duration of anesthesia increase, while the delay of onset decreases. In general, the fastest onset and shortest duration of anesthesia occurs with spinal or subcutaneous injections; a slower onset and longer duration are obtained with plexus blocks (11). Epinephrine is frequently added to LA solutions in a 1:200,000 dilution (5 μg/mL) to cause vasoconstriction, decreasing vascular absorption of the LA, permitting more effective and more prolonged anesthesia, and to serve as a marker for intravascular injection (2,4). Other popular LA additives include clonidine, opioids, neostigmine, hyaluronidase, and $NaHCO_3$.

H^+ ions have complex interactions with LAs. LAs block action potentials more potently at basic pH, where there are increased amounts of LA in the uncharged form, than at more acid pH values (Fig. 3) (12,13). LA bases diffuse across the nerve sheath and nerve membrane more readily than charged LAs, hastening onset of anesthesia. Indeed, some clinical studies show that the addition of sodium bicarbonate to LAs speeds the onset of nerve blocks (2,4). Curiously, once LAs gain access to the cytoplasmic side of the Na

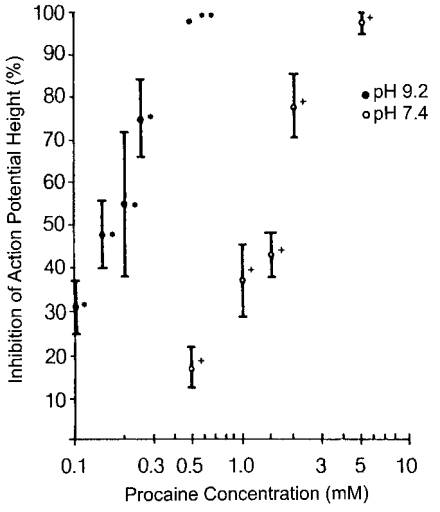

Figure 3. Effect of pH on potency of procaine in isolated nerves (*n = 3, +n = 4, **n = 5) (from Anesthesiology 1988;68:501–6).

channel, H^+ ions potentiate use-dependent block (3,5). LA solutions prepackaged with epinephrine have an acidic pH to retard oxidation of the epinephrine; these solutions show larger increases in pH and in speed of onset with $NaHCO_3$ than epinephrine-free solutions.

Spread of epidural or spinal anesthesia increases during pregnancy (14). Pregnancy appears to increase the susceptibility of nerves to LAs (Fig. 4) (15).

LA Concentrations, Protein Binding, Metabolism, and Pharmacokinetics

During regional anesthesia, LAs are applied to their target site; almost all other drugs must be delivered by bloodflow to their target sites. Peak LA concentrations vary by the site of injection. When the same LA dose was administered, increasing peak LA concentrations were measured after plexus, epidural, and intercostal blocks, respectively (2,4,11).

In blood, all LAs are partially protein-bound, primarily to α_1-acid glycoprotein and secondarily to albumin (1,2,4). The least potent, shortest-acting LAs are less protein-bound than the more potent, longer-persisting agents. Protein binding decreases during pregnancy (16). LA protein binding approaches saturation only at very increased drug concentrations (17).

Metabolism converts relatively lipid-soluble LAs into smaller, more water-soluble compounds. For esters, the primary step is ester hydrolysis, catalyzed by plasma pseudocholinesterase. The rate of hydrolysis is rapid, yielding half-lives measured in seconds for procaine (1,2,4). Procaine and benzocaine are metabolized to para-aminobenzoic acid (PABA), the species underlying anaphylaxis to these agents (2). Chloroprocaine and tetracaine are metabolized similarly, but not to PABA (2,4).

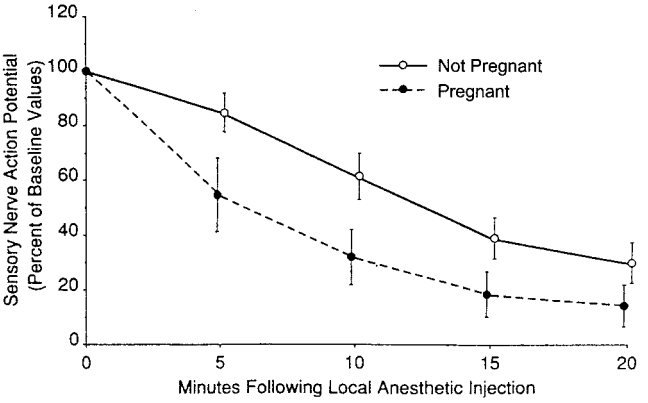

Figure 4. Effect of pregnancy on lidocaine inhibition of median nerve fibers (from Anesthesiology 1990;72:962–5).

The amides undergo nearly exclusive metabolism by the cytochrome P450 enzymes in the liver. Little (<5%) of these agents is excreted unchanged in urine. Lidocaine undergoes oxidative N-dealkylation (1,2,4). Bupivacaine, ropivacaine, mepivacaine, and etidocaine also undergo N-dealkylation and hydroxylation (1,2,4). Prilocaine undergoes hydrolysis to o-toluidine, a by-product that (directly or indirectly through hydroxylation products) causes methemoglobinemia (2,9). Traditional teaching is that the prilocaine dose must exceed 600 mg in adults to produce significant methemoglobinemia that, in any case, is easily treated with IV methylene blue (1 mg/kg).

Ester metabolism theoretically can be slowed by cholinesterase deficiency or cholinesterase inhibition, but specific data are largely lacking. Because all amides are metabolized in the liver, drug clearance is highly dependent on hepatic blood flow, hepatic extraction, and enzyme function (1,2,4). There is considerable first-pass uptake of LAs by lung (18). Amide LA clearance is reduced by factors that decrease hepatic blood flow, such as β-adrenergic receptor or H_2-receptor blockers, or by heart or liver failure (1,2,4).

Local Anesthetic Toxicity

Central Nervous System (CNS) Side Effects. The initial manifestations of LA CNS toxicity reflect disinhibition and excitation of the CNS (1,2,4,11). As the dose increases, humans experience a stereotypical sequence of signs and symptoms, which may progress to seizures. In animal experiments, when LA dosing continues, CNS excitation progresses to CNS depression, with eventual respiratory arrest. Potent LAs consistently produce seizures at lower blood concentrations and lower doses than less potent LAs. Both elevated Pco_2 and metabolic acidosis decrease the LA convulsive dose (19).

Cardiovascular Toxicity. Most LAs will not produce cardiovascular (CV) toxicity until the blood concentration is at least three times that producing seizures;

however, there are reports of simultaneous CNS and CV toxicity with bupivacaine and related agents (1,2,4). LA CV toxicity may result from LA actions on the heart or on the peripheral circulation.

LAs bind and inhibit cardiac Na channels (1,5). Bupivacaine binds more avidly and for a longer duration to cardiac Na channels than lidocaine (20). The bupivacaine R(+) isomer binds cardiac Na channels more avidly than the S(-) isomer, forming the basis for the development of ropivacaine and levobupivacaine. LAs produce dose-dependent myocardial depression (21). LA doses producing CV collapse reflect their rank order of potency at producing nerve block (21,22).

LAs bind and inhibit cardiac Ca and K channels at concentrations greater than those at which binding to Na channels is maximal (3,5,23). LAs bind β-adrenergic receptors and inhibit the ability of epinephrine to stimulate cyclic AMP formation (24,25). This could underlie the refractoriness of bupivacaine CV toxicity to standard resuscitation measures.

In dogs, programmed electrical stimulation (PES) elicited more PVCs with bupivacaine and levobupivacaine than with lidocaine or ropivacaine (26,27). When given to the point of CV collapse, the LAs differed. Animals receiving lidocaine could be resuscitated, but required continuing infusion of epinephrine to counteract the continuing LA-induced myocardial depression. If animals receiving the longer acting agents could be resuscitated, they usually did not require continuing therapy (26,27). At very low concentrations LAs inhibit nitric oxide release, causing vasoconstriction (28). LAs administered IV cause dose-dependent decreases in systemic vascular resistance. LAs injected in the skin usually produce vasodilation (29). Cocaine is the only LA that consistently produces local vasoconstriction.

Allergic Reactions to LAs. True allergic reactions to LAs are uncommon. Accidental IV injections of LA are commonly misdiagnosed as allergic reactions. True anaphylaxis has been documented with esters, particularly those metabolized directly to PABA. Anaphylaxis to amide anesthetics is much less common (30). Some reactions may result from allergy to a preservative. When time permits, patients presenting with LA allergy can have skin testing to determine nonreactive agents.

Neurotoxic Effects of LAs. During the 1980s, 2-chloroprocaine occasionally was associated with cauda equina syndrome when large doses (formulated with Na metabisulfite at an acidic pH) were accidentally injected into spinal fluid (2,4). Reports of neurotoxicity virtually disappeared when the compound was reformulated, but returned following the introduction of a generic product containing the original metabisulfite and pH. Presently, there is controversy regarding whether lidocaine produces persisting sacral deficits and whether it may be associated with an excessive incidence of transient radicular irritation after spinal anesthesia. Five percent lidocaine, unlike other spinal LA solutions, will permanently interrupt nerve conduction when applied to isolated nerves (31).

Treatment of LA Toxicity

Treatment of adverse reactions depends on their severity. Minor reactions can be allowed to terminate spontaneously. Essential treatment of LA-induced seizures should include maintaining the airway and providing oxygen. Seizures may be terminated with IV thiopental (1–2 mg/kg), benzodiazepines (midazolam 0.05–0.10 mg/kg), or a paralytic dose of succinylcholine (0.5–1 mg/kg) followed by tracheal intubation (2). If LA intoxication produces CV depression, hypotension may be treated by infusion of IV fluids and vasopressors (phenylephrine 0.5–5 μg/kg/min or norepinephrine 0.02–0.2 μg/kg/min). If myocardial failure is present, IV epinephrine (1–15 μg/kg IV bolus) may be required. When toxicity progresses to cardiac arrest, the guidelines for Advanced Cardiac Life Support should be followed.

References

1. Strichartz GR, ed. Local anesthetics: handbook of experimental pharmacology. Heidelberg: Springer-Verlag, 1987.
2. de Jong RH. Local anesthetics. St. Louis. Mosby-Year Book, Inc., 1994.
3. Butterworth JF, Strichartz GR. Molecular mechanisms of local anesthesia: a review. Anesthesiology 1990;72:711–34.
4. Tetzlaff J. Clinical pharmacology of local anesthetics. Woburn, MA: Butterworth-Heinemann, 2000.
5. Hille B. Ionic channels of excitable membranes. 2nd ed. Sunderland, MA: Sinauer Associates, Inc., 1992.
6. Wang SY, Nau C, Wang GK. Residues in Na(+) channel D3-S6 segment modulate both batrachotoxin and local anesthetic affinities. Biophys J 2000;79:1379–87.
7. Sugimoto M, Uchida I, Fukami S, et al. The alpha and gamma subunit-dependent effects of local anesthetics on recombinant GABA(A) receptors. Eur J Pharmacol 2000;401:329–37.
8. 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. Anesth Analg 1987;66:159–65.
9. Strichartz GR, Sanchez V, Arthur GR, et al. Fundamental properties of local anesthetics. II. Measured octanol:buffer partition coefficients and pKa values of clinically used drugs. Anesth Analg 1990;71:158–70.
10. Butterworth J, Ririe DG, Thompson RB, et al. Differential onset of median nerve block: randomized, double-blind comparison of mepivacaine and bupivacaine in healthy volunteers. Br J Anaesth 1998;81:515–21.
11. Covino BG, Vasallo HG. Local anesthetics. New York: Grune & Stratton, 1976.
12. Butterworth JF IV, Lief PA, Strichartz GR. The pH-dependent local anesthetic activity of diethylaminoethanol, a procaine metabolite. Anesthesiology 1988;68:501–6.

13. Ririe DG, Walker FO, James RL, et al. Effect of alkalinization of lidocaine on median nerve block. Br J Anaesth 2000;84:163–8.
14. Fagraeus L, Urban BJ, Bromage PR, et al. Spread of epidural analgesia in early pregnancy. Anesthesiology 1983;58:184–7.
15. Butterworth JF IV, Walker FO, Lysak SZ. Pregnancy increases median nerve susceptibility to lidocaine. Anesthesiology 1990; 72:962–5.
16. Fragneto RY, Bader AM, Rosinia F, et al. Measurements of protein binding of lidocaine throughout pregnancy. Anesth Analg 1994;79:295–7.
17. Thomas JM, Schug SA. Recent advances in the pharmacokinetics of local anaesthetics: long-acting amide enantiomers and continuous infusions. Clin Pharmacokinet 1999;36:67–83.
18. Rothstein P, Arthur GR, Feldman HS, et al. Bupivacaine for intercostal nerve blocks in children: blood concentrations and pharmacokinetics. Anesth Analg 1986;65:625–32.
19. Englesson S, Grevsten S. The influence of acid-base changes on central nervous system toxicity of local anaesthetic agents. II. Acta Anaesthesiol Scand 1974;18:88–103.
20. Chernoff DM. Kinetic analysis of phasic inhibition of neuronal sodium currents by lidocaine and bupivacaine. Biophys J 1990; 58:53–68.
21. Feldman HS, Covino BM, Sage DJ. Direct chronotropic and inotropic effects of local anesthetic agents in isolated guinea pig atria. Reg Anesth 1982;7:149–56.
22. Reiz S, Nath S. Cardiotoxicity of local anaesthetic agents. Br J Anaesth 1986;58:736–46.
23. McCaslin PP, Butterworth J. Bupivacaine suppresses [Ca^{2+}](i) oscillations in neonatal rat cardiomyocytes with increased extracellular K^+ and is reversed with increased extracellular Mg^{2+}. Anesth Analg 2000;91:82–8.
24. Butterworth JF IV, Brownlow RC, Leith JP, et al. Bupivacaine inhibits cyclic-3',5'-adenosine monophosphate production: a possible contributing factor to cardiovascular toxicity. Anesthesiology 1993;79:88–95.
25. Butterworth J, James RL, Grimes J. Structure-affinity relationships and stereospecificity of several homologous series of local anesthetics for the beta2-adrenergic receptor. Anesth Analg 1997;85:336–42.
26. Groban L, Deal DD, Vernon JC, et al. Ventricular arrhythmias with or without programmed electrical stimulation after incremental overdosage with lidocaine, bupivacaine, levobupivacaine, and ropivacaine. Anesth Analg 2000;91:1103–11.
27. Groban L, Deal DD, Vernon JC, et al. Cardiac resuscitation after incremental overdosage with lidocaine, bupivacaine, levobupivacaine, and ropivacaine in anesthetized dogs. Anesth Analg 2001;92:37–43.
28. Johns RA. Local anesthetics inhibit endothelium-dependent vasodilation. Anesthesiology 1989;70:805–11.
29. Carpenter RL, Kopacz DJ, Mackey DC. Accuracy of laser Doppler capillary flow measurements for predicting blood loss from skin incisions in pigs. Anesth Analg 1989;68:308–11.
30. deShazo RD, Nelson HS. An approach to the patient with a history of local anesthetic hypersensitivity: experience with 90 patients. J Allergy Clin Immunol 1979;63:387–94.
31. Lambert LA, Lambert DH, Strichartz GR. Irreversible conduction block in isolated nerve by high concentrations of local anesthetics. Anesthesiology 1994;80:1082–93.