CHAPTER 2: LOCAL ANESTHETICS

LOCAL ANESTHETICS

The resting potential of the cell membrane is negative (-70 mV) and close to the potential determined by potassium alone. During transmission of an action potential, Na^+ moves into the cell through open Na^+ channels depolarizing the membrane and bringing its potential to -20 mV or more.

Local anesthetics are compounds that have the ability to interrupt the transmission of the action potential in excitable membranes by binding to specific receptors in the Na^+ channels. This action, at clinically recommended doses, is reversible. Conduction can still continue, although at a slower pace, with up to 90% of receptors blocked.

All local anesthetics are potentially neurotoxic if injected intraneurally, especially if that injection is intrafascicular. The neuronal damage may be directly related to the degree of hydrostatic pressure reached inside the axoplasma. Local anesthetics injected around nerves could also be toxic as result of the concentration of the agent and the duration of the exposure (e.g., cauda equina after intrathecal local anesthetics).

The local anesthetics available in clinical practice are usually racemic mixtures, a mixture of both D (dextrorotatory, also called R) and L (levorotatory, also called S) enantiomers. Exceptions are lidocaine, levobupivacaine and ropivacaine. The L (or S) enantiomer appears to have similar local anesthetic efficacy than the D (or R) enantiomer, but lesser cardiac toxicity.

Historical perspective

Anesthesia by compression was common in the antiquity. Cold as an anesthetic was widely used until the 1800s. The native Indians of Peru chewed coca leaves and knew about their cerebral-stimulating effects and possibly about their local anesthetic properties (there are some reports of natives using an emulsion of chewed coca leaves and saliva on wounds). The leaves of ***erythroxylon coca*** were taken to Europe where Niemann in Germany isolated cocaine in 1860.

Carl Koller, a contemporary and friend of Sigmund Freud, is credited with the introduction of cocaine as a topical ophthalmic local anesthetic in Austria in 1884. In 1888 Koller came to the United States and established a successful ophthalmology practice at Mount Sinai Hospital in New York until the year of his death in 1944.

Recognition of cocaine's cardiovascular side effects, as well as its potential for dependency and abuse, led to a search for better local anesthetic drugs. Cocaine is a good topical local anesthetic that also produces vasoconstriction and for this reason it is still used, by some, as a topical anesthetic in the nose and other mucous membranes. Cocaine blocks the reuptake of cathecolamines from nerve endings. Total dose should not exceed 100 mg (2.5 mL of a 4% solution), to avoid systemic effects like hypertension, tachycardia and cardiac arrhythmias.

Ropivacaine is the only other local anesthetic able to produce some vasoconstriction, and that effect is weak.

Highlights on local anesthesia and related issues

1850s Invention of the syringe and hypodermic hollow needle.
1884 Halsted, an American surgeon, blocks the brachial plexus with a solution of cocaine under direct surgical exposure.
1885 Wood, in the United Kingdom, is credited with the introduction of conduction anesthesia through a hypodermic injection.
1897 Epinephrine is isolated by John Abel at Johns Hopkins Medical School.
1897 Braun in Germany relates cocaine toxicity with systemic absorption and advocates the use of epinephrine.
1898 Bier is set to receive the first planned spinal anesthesia from his assistant Hildebrandt. After CSF is obtained, the syringe is found not to fit the needle and therefore the spinal is not completed. Bier in turn successfully performs the first spinal anesthesia on Hildebrandt using cocaine. Subsequently both experienced the first spinal headaches.
1908 Bier introduces the intravenous peripheral nerve block (Bier block) with procaine.
1911 Hirschel performs the first percutaneous axillary block.
1911 Kulenkampff performs the first percutaneous supraclavicular block.
1922 Gaston Labat of France, a disciple of Pauchet, introduces in the US his book "Regional Anesthesia Its Technic and Clinical Application", the first manual of regional anesthesia published in America.
1923 Labat establishes the first American Society of Regional Anesthesia.
1953 Daniel Moore, practicing at Virginia Mason Clinic in Seattle, publishes his influential book "Regional Block".
1975 Alon Winnie, L. Donald Bridenbaugh, Harold Carron, Jordan Katz, and P. Prithvi Raj establish the current American Society of Regional Anesthesia (ASRA) in Chicago.
1976 The first ASRA meeting is held in Phoenix, Arizona.
1976 Regional Anesthesia Journal, volume 1, number 1 is published.
1983 Winnie introduces his book, Plexus Anesthesia, Perivascular Techniques of Brachial Plexus Block.

Date of introduction in clinical practice of some local anesthetics:

1905 procaine; 1932 tetracaine; 1947 lidocaine; 1955 chloroprocaine (last ester still in use); 1957 mepivacaine; 1963 bupivacaine; 1997 ropivacaine; 1999 levobupivacaine.

Chemical structure of local anesthetics

Local anesthetics are weak bases with a pka above 7.4 and poorly soluble in water. They are commercially available as acidic solutions (pH 4-7) of hydrochloride salts, which are hydrosoluble. A typical local anesthetic molecule is composed of two parts, a benzene ring (lipid soluble, hydrophobic) and an ionizable amine group (water soluble, hydrophilic). These two parts are linked by a chemical chain, which can be either an ester (-CO-) or an amide (-HNC-). This is the basis for the classification of local anesthetics as either **esters or amides**.

Injecting local anesthetics in the proximity of a nerve(s) triggers a sequential set of events, which eventually culminates with the interaction of some of their molecules with receptors located in the Na^+ channels of nerve membranes. The injected local anesthetic volume spreads initially by **mass movement**, moving across "points of least resistance", which unfortunately do not necessarily lead into the desired nerve(s). This fact emphasizes the importance of injecting in close proximity of the target nerve(s). The local anesthetic solution then **diffuses** through tissues; each layer acting as a physical barrier. In the process part of the solution gets **absorbed** into the circulation. Finally a small percentage of the anesthetic reaches the target nerve membrane, at which point the different physicochemical properties of the individual anesthetic become the factors dictating the speed, duration and nature of the interaction with the receptors.

Physicochemical properties-activity relationship

1. **Lipid solubility:** determines both the potency and the duration of action of local anesthetics, by facilitating their transfer through membranes and by keeping the drug close to the site of action and away from metabolism. In addition, the local anesthetic receptor site in Na^+ channels is thought to be hydrophobic, so its affinity for hydrophobic drugs is greater. Hydrophobicity also increases toxicity, so the therapeutic index of more lipid soluble drugs is decreased.

2. **Protein binding:** local anesthetics are bound in large part to plasma and tissue proteins. The bound portion is not pharmacologically active. The plasmatic unbound fraction is responsible for systemic toxicity. The most important binding proteins in plasma are albumins and alpha-1-acid glycoprotein (AAG). Although albumin has a greater binding capacity than AAG, the latter has a greater affinity for drugs with pka higher than 8, the case for most local anesthetics. Newborn infants have very low concentration of AAG, only reaching adult values by 10 months of age. The elderly and debilitated also frequently have decreased levels of albumin and other plasma proteins. These patient populations could be at increased risk for toxicity.

   On the other hand, AAG levels increase during stress and for several days after the postoperative period. Higher levels of AAG lead to decreased levels of unbound fraction of

local anesthetics and a decreased potential for local anesthetic toxicity. However, changes in protein binding are only clinically important for drugs highly protein-bound, such as bupivacaine, which is 96% bound, and sufentanil and alfentanil, which are both 92% bound (Booker et al, Br J Anaesth 1996).

The fraction of drug bound to protein in plasma correlates with the duration of action of local anesthetics: ***bupivacaine (95%) = ropivacaine (94%)> tetracaine (85%) > mepivacaine (75%) > lidocaine 65%) > procaine (5%) and 2-chloroprocaine (negligible).*** This suggests that the binding site for the local anesthetic molecule in the sodium channel receptor protein, may share a similar sequence of amino acids with the plasma protein binding site.

Drugs as lidocaine, tetracaine, bupivacaine and morphine (e.g., DepoDur) have been incorporated into liposomes to prolong their duration of action. Liposomes are vesicles with two layers of phospholipids, which slow down the release of the drug.

3. **Pka:** determines the ratio between the ionized (cationic) and the uncharged (base) forms of the drug. The pka of local anesthetics ranges from 7.6 to 9.2. By definition the pka is the pH at which 50% of the drug is ionized and 50% is present as a base. The pka generally correlates with the speed of onset of most local anesthetics. The closer the pka is to physiologic pH, the faster the onset. For example, lidocaine with a pka of 7.7 is 25% non-ionized at pH 7.4. Its onset is therefore faster than bupivacaine, whose pka of 8.1 makes it only 15% non-ionized at that pH. One important exception is 2-chloroprocaine that, despite its pka of 9.1, has a very rapid onset. This is usually attributed to the relatively high concentrations (3%) used in clinical practice that are possible thanks to its low toxicity. It has also been claimed that 2-chloroprocaine has better "tissue penetrability".

Mechanism of action and sodium channels

The non-charged hydrophobic fraction (B), which exists in equilibrium with the hydrophilic charged portion (BH^+), crosses the lipidic nerve membrane and initiates the events that lead to Na^+ channel blockade. Once inside the cell, the pka of the drug and the intracellular pH dictate a new equilibrium between the two fractions. Because of the relative more acidic intracellular environment, the relative proportion of charged fraction (BH^+) increases. This hydrophilic, charged fraction is the active form on the Na^+ channel.

The Na^+ channel is a protein structure that communicates the extracellular of the nerve with its axoplasm. It consists of four repeating alpha subunits and two beta subunits, beta-1 and beta-2. The **alpha** subunits are involved in ion movement and **local anesthetic activity**. It is generally accepted that the main action of local anesthetics involves interaction with specific binding sites within the Na^+ channel. Local anesthetics **may also block** to some degree **calcium** and **potassium** channels as well as **N-methyl-D-aspartate (NMDA)** receptors. Local anesthetics do not ordinarily affect the membrane resting potential.

The Na^+ channels seem to exist in three different states, closed (resting), open and inactivated. Under adequate stimulation, the protein molecules of the channel undergo conformational changes, from the resting state to the ion-permeable state or open state, allowing the inflow of extracellular Na^+, which depolarizes the membrane. After a few milliseconds the channel goes then through a transitional inactivated state, where the proteins leave the channel closed and ion-impermeable. With repolarization the proteins revert to their resting configuration.

Other drugs, like tricyclic antidepressants (amitriptyline), meperidine, volatile anesthetics and ketamine, also exhibit Na^+ channel-blocking properties. Tetrodotoxin and other biotoxins also interact with the Na^+ channels, although their actions are exerted on the extracellular side of the channel.

Frequency-dependent blockade

Local anesthetics show more affinity for open Na^+ channels. When a nerve is experiencing a high frequency of depolarization, like during spontaneous pain or voluntary muscle contractions, it becomes more sensitive to blockade, because the chances of interaction, between local anesthetics molecules and Na^+ channels, increase.

The concept of frequency-dependent blockade also explains the greater susceptibility to blockade exhibited by small sensory fibers, as they generate long action potential (5 ms) at high frequency. Motor fibers on the other hand generate short action potentials (0.5 ms) at lower frequency making them more difficult to block.

Pregnancy and local anesthetics

Increased sensitivity to local anesthetics, demonstrated as faster onset and more profound block, may be present during pregnancy. Alterations in protein binding of bupivacaine may result in increased concentrations of active unbound drug in the pregnant patient, increasing its potential for toxicity.

Placental transfer is also more active for lipid soluble local anesthetics. In any case, agents with a pka closer to physiologic pH have a higher placental transfer. As a result, the umbilical vein/maternal vein ratio for mepivacaine (pka 7.6) is 0.8, while for bupivacaine (pka 8.1) is 0.3.

In the presence of fetal acidosis, local anesthetics cross the placenta and become ionized in higher proportion than at normal pH. The ionized fraction cannot cross back to the maternal circulation, originating what is called **“ion trapping”.** Therefore, 2-chloroprocaine, with its very short maternal and fetal half-lives, is an ideal local anesthetic in the presence of fetal acidosis.

Fiber size and pattern of blockade

As a general rule small nerve fibers are more susceptible to local anesthetics than large fibers. However, other factors like myelinization and relative position of the fibers within a nerve (mantle versus core) may also play a role. The depolarization in myelinated fibers is saltatory. About three nodes of Ranvier need to be blocked in order to block the transmission of the action potential.

The smallest nerve fibers are non-myelinated and are blocked more readily than larger myelinated fibers. However at similar size, myelinated fibers are blocked before non-myelinated fibers. In general, autonomic fibers, small non-myelinated C fibers (mediating pain, temperature and touch), and small myelinated A delta fibers (mediating pain and cold temperature) are blocked before A alpha, A beta and A gamma fibers (motor, propioception, touch, and pressure).

It has been speculated that in large nerve trunks, motor fibers would be usually located in the outer portion (mantle) of the nerve bundle, therefore more "accessible" to local anesthetics. This would help explain why motor fibers tend to be blocked before sensory fibers in large mixed nerves. In contrast, the frequency-dependence of local anesthetic action would favor block of small sensory fibers, as they generate long action potentials at high frequency, whereas motor fibers generate short action potentials at lower frequency.

Fiber Type	Sensory Classification	Modality Served	Diameter (mm)	Conduction (m/s)	Local Anesthetic Sensitivity	Myelination
Aα		Motor	12–20	70–120	+	Yes
Aα	Type Ia	Proprioception	12–20	70–120	++	Yes
Aα	Type Ib	Proprioception	12–30	70–120	++	Yes
Aβ	Type II	Touch pressure Proprioception	5–12	30–70	++	Yes
Aγ		Motor (muscle spindle)	3–6	15–30	++	Yes
Aδ	Type III	Pain Cold temperature Touch	2–5	12–30	+++	Yes
B		Preganglionic autonomic fibers	< 3	3–14	++++	Some
C Dorsal root	Type IV	Pain Warm and cold temperature Touch	0.4–1.2	0.5–2	++++	No
C Sympathetic		Postganglionic sympathetic fibers	0.3–1.3	0.7–2.3	++++	No

[1]Peripheral nerve fibers and their respective neurons are classified from A to C according to axonal diameter, covering (myelinated or unmyelinated), and conduction velocity. Sensory fibers also are categorized as I–IV. Type C (sensory type IV) are unmyelinated fibers, whereas type Aδ fibers are lightly myelinated.

(Figure from Morgan's Clinical Anesthesiology, 3rd edition, 2006, reproduced with permission)

Modulating local anesthetic action

pH adjustment by addition of bicarbonate

The ionized fraction of local anesthetics is the active form in the Na^+ channel, although the rate-limiting step in this cascade is determined by membrane penetration of local anesthetics in its non-ionized (lipophilic) form. Unfortunately, only a small proportion of local anesthetic in solution exists in the non-ionized state. An increased pH may theoretically reduce the onset time of local anesthetics by increasing the proportion of its non-ionized fraction. At a pH of 5.0 to 5.5 the cation/base ratio is 1000:1, while at a pH of 7.4 the same ratio becomes 60:40. The limiting factor for pH adjustment is the solubility of the base form before reaching precipitation. The most lipid soluble agents, like bupivacaine and ropivacaine, cannot be alkalinized above a pH of 6.5 because they precipitate.

DiFazio et al (Anesth Analg, 1986) demonstrated a more than 50% decrease in onset of epidural anesthesia, when the pH of commercially available lidocaine with epinephrine was raised from 4.5 to 7.2, by the addition of bicarbonate. Capogna et al (Reg Anesth, 1995) randomized 180 patients to study the effects of alkalinizing lidocaine, mepivacaine and bupivacaine for nerve blocks. They concluded that alkalinization of lidocaine and bupivacaine shortens the onset of epidural; alkalinization of lidocaine shortens the onset of axillary block and alkalinization of mepivacaine shortens the onset of sciatic/femoral blocks. However, when only small changes in pH can be achieved, because of the limited solubility of the base, only small decreases in onset time will occur, as when plain bupivacaine is alkalinized. It has been claimed that adding bicarbonate to local anesthetics containing epinephrine added by the manufacturer may speed the onset of action because those vials have a lower pH, and that the effect would be negligible when fresh epinephrine is added to a plain solution.

I believe that even in cases in which bicarbonate has shown to speed the onset of action of some local anesthetics in some locations (mainly epidural), this slight faster onset might be statistically but not clinically significant. On the other hand, the time it takes to find and add bicarbonate needs to be subtracted from whatever small gain in onset is obtained as a result. Other than adding bicarbonate to speed the onset of epidural in obstetrics (i.e., epidural "top off" for emergency C-section) I don't think bicarbonate has other uses in regional anesthesia.

Carbonation

Another approach to shortening onset time has been the use of carbonated local anesthetic solutions. These solutions contain large amounts of carbon dioxide, which readily diffuses into the axoplasm of the nerve, lowering the pH and favoring the formation of the cationic active form of the local anesthetic inside the cell. Carbonated solutions are not available in the United States.

LOCAL ANESTHETICS ADDITIVES

Vasoconstrictors

Epinephrine is the most common vasoconstrictor added to local anesthetics to prolong the anesthetic effect and to decrease absorption. Epinephrine is also used to detect intravascular injection. Without beta-blockers on board, 15 mcg of epinephrine should produce a 30% increase in heart rate within 30 seconds.

Vasoconstrictors may also improve the quality and density of the block, especially with spinal and epidural anesthesia. This has been demonstrated with tetracaine, lidocaine and bupivacaine. The mechanism is unclear. Epinephrine may simply increase the amount of local anesthetic available by reducing absorption. It could also have some local anesthetic effect by means of its α2-agonist actions. **Subarachnoid epinephrine also delays voiding and discharge readiness.**

The prolongation of effect in peripheral nerve blocks can be 30-60%, depending on site of injection and type of local anesthetics (more vascular sites like intercostal see more effect, and intermediate agents like lidocaine benefit more). Peripherally epinephrine does not have any significant alpha-2 effect.

In general, epinephrine added to spinal anesthesia prolongs the effect of the less lipid soluble agents like lidocaine and mepivacaine (20-30%). The exception to this rule is tetracaine,

a highly lipid soluble agent, that gets the largest prolongation of all spinal local anesthetics (up to 60% in lumbar dermatomes).

The usual dose of intrathecal epinephrine is 200 mcg, but doses as small as 50 mcg can be sufficient. In the epidural space the usual dose is 5 mcg/mL. Epinephrine, other than intrathecal, is absorbed systemically and may produce adverse cardiovascular effects. In small doses the beta-adrenergic effects predominate, with increased cardiac output and heart rate. Dose larger than 0.25 mg (250 mcg) may be associated with arrhythmias or other undesirable cardiac effects.

The potential risk for peripheral nerve ischemia, as a result of epinephrine acting on epineural vessels and vaso nervorum has to be balanced against the lower risk of systemic toxicity, the ability to detect intravascular injection and the prolongation of action. According to Neal (Reg Anesth Pain Med 2003) adding 5 mcg/mL (1:200,000 dilution) prolongs the duration of lidocaine for peripheral nerve blocks from 186 min to 264 min. Adding only 2.5 mcg/mL (1:400,000 dilution) prolongs the block about the same (240 min) without apparent effect on nerve blood flow. Patients with micro angiopathy (e.g., diabetics), who could be at increased risk for neural ischemia, potentially could benefit from the use of more diluted epinephrine. In 2006 Bigeleisen published in Anesthesiology a report of intentional intraneural injection guided by ultrasound in 72 out of 104 nerves in the axilla. He injected a combination of bupivacaine/lidocaine solution containing 3 mcg/mL of epinephrine. The author did not report any evidence of nerve injury in a 6-month follow up period.

Intrathecal epinephrine does not lead to cord ischemia, because it does not decrease spinal cord blood flow, although it decreases epidural blood flow (Kosody R, et al, 1984). In fact spinal cord ischemia due to epinephrine is "improbable because the cord vessels are autoregulated and show very minimal response to endogenous or exogenous vasoactive agents" (Neal JM In: Regional Anesthesia, The Requisites. Elsevier Mosby, Philadelphia 2004)

Although epinephrine-containing local anesthetics are usually contraindicated in areas of terminal circulation (e.g., digits) this recommendation is not based on hard evidence. Anecdotal use of epinephrine-containing solutions in digits is cited in the literature. Lalonde et al for example published in 2005 a multicenter study including 3,110 consecutive cases of use of epinephrine in the fingers and hand from 2002 to 2004. The authors (surgeons) defined "low dose" epinephrine as 1:100,000 and they reported no instance "of digital tissue loss" (J Hand Surg, 2005). This is an interesting piece of clinical evidence, although at this time this is not a recommended practice.

The 2010 ASRA Practice Advisory on Local Anesthetic Systemic Toxicity states that the use of epinephrine as an intravascular marker, although not perfect, is recommended because its benefits likely outweigh its risks in the majority of patients. Adding 1:400,000 epinephrine as an intravascular marker to local anesthetic solutions for nerve blocks is the standard in our practice, in all sort of nerve blocks and patients, both diabetics and non-diabetics.

Dilution/concentration issues

By definition a 1:1,000 dilution means 1 g solute in 1,000 mL of solution. That is 1,000 mg in 1,000 mL or 1 mg/mL or 1,000 mcg/mL

Therefore, if 1:1,000 equals 1,000 mcg/mL, then:

- 1:10,000 equals 100 mcg/mL
- 1:100,000 equals 10 mcg/mL
- 1:200,000 equals 5 mcg/mL
- 1:400,000 equals 2.5 mcg/mL

Opioids

1. **Neuraxial use:** The addition of opioids to local anesthetics has a synergistic effect, both in anesthesia and postoperative analgesia (especially visceral pain). They block pain pathways without significantly affecting motor or sympathetic fibers.
   The hydrophilic opioid morphine can be used in doses of 0.1-0.3 mg spinal and 1-3 mg epidural. It has a slow onset of around 45 min, providing an analgesic action that lasts 12-24 h. Morphine reaches the brainstem and 4th ventricle slowly. Delayed respiratory depression (8-10 h) is a risk with all neuraxial opioids, but it is more frequently seen with hydrophilic drugs like morphine, and in susceptible populations like the elderly and debilitated. Neuraxial morphine is also associated with higher incidence (40-50%) of nausea and vomiting than systemic opioids, more pruritus (60-80%, 20% of it severe), and delayed voiding. It is not suitable for outpatients.
   Short-acting opioids, such as fentanyl and sufentanil, when added to spinal anesthetics can also intensify the block, and prolong the duration of anesthesia, beyond the duration of local anesthetics. Respiratory depression with these agents is rare and usually early (within 4 h). Sufentanil spinal can be used in doses of 2.5-10 mcg. Fentanyl spinal is used in doses of 10-25 mcg and 25-150 mcg epidural. Onset occurs at 5-15 min, peak effect at 10-20 min and duration of 1-3 h. Hypotension, pruritus, nausea and vomiting are some common side effects.

   Extended-release epidural morphine (DepoDur): it is a liposomal formulation designed for epidural use, providing 48 h of pain relief. DepoDur was approved for clinical use in 2004. It is supplied in a 2 mL vial containing 10 mg/mL dose in sterile saline. It is only approved as a single **lumbar epidural** dose prior to surgery or after clamping of the umbilical cord during C-section. The recommended dose is 10 mg for C-section, 10-15 mg for lower abdominal surgery and 15 mg for major orthopedic surgery of the lower extremities. Respiratory depression is dose-related. The most common adverse events reported during clinical trials were decreased oxygen saturation, hypotension, urinary retention, nausea and vomiting, constipation and pruritus.

2. **Peripheral nerve blocks**: The usefulness of opioids in peripheral nerve blocks is mostly unsupported by the evidence. Opioids have been shown useful when injected intra-articularly.

Clonidine

Alpha-2 agonists have central (sedation, analgesia, bradycardia) and peripheral effects (vasoconstriction/vasodilation with net hypotension, anti shivering, diuresis). The site for sedative action is the locus ceruleus of the brain stem, while the principal site for analgesia seems to be the spinal cord.

The main alpha-2 effect on the heart is decreased tachycardia by blocking cardioacelerator fibers, and bradycardia through a vagomimetic effect. In the periphery clonidine produces both vasodilation via sympatholysis and vasoconstriction through receptors on smooth muscle. The cause for its anti shivering and diuretic effects are yet to be established.

Side effects, including sedation, hypotension and bradycardia limit the clinical usefulness of alpha-2 agonists. Small doses of clonidine (50-75 mcg) have shown to significantly prolong analgesia in spinal, epidural, IV regional, and peripheral nerve blocks, both when injected along local anesthetics and when given orally. Unlike epinephrine clonidine does not prolong motor block. Injected intrathecally, it can also delay voiding and can produce orthostasis. Side effects are not as often with clonidine doses of less than 1.5 mcg/kg or a total dose of less than 150 mcg.

In 2001 Iskandar et al in France showed that adding 50 mcg of clonidine to selected nerves (median and musculocutaneous) prolonged mepivacaine sensory anesthesia by 50%, compared to placebo, after a mid-humeral block, without prolonging motor effect. Because the prolongation was observed only in the nerves that received clonidine they postulated that the effect must be peripheral and not central through absorption.

Dexmedetomidine

It is a more selective alpha-2 agonist agent with an alpha-2:alpha-1 receptor ratio of 1,600:1, seven times greater than that of clonidine. Its elimination half-life is only 2 h compared to more than 8 h for clonidine. Dexmedetomidine may offer extended analgesia with lesser side effects. This drug is gaining popularity as a sedative both in the ICU and the OR.

Neostigmine

It is an acetylcholinesterase inhibitor that prevents the breakdown of acetylcholine promoting its accumulation. Acetylcholine is an endogenous spinal neurotransmitter that induces analgesia. Neostigmine does not cause neural blockade nor have any action on opioid receptors.

Spencer Liu et al (Anesthesiology, 1999) studied the effects of different doses of neostigmine added to bupivacaine spinal. They reported that 50 mcg of neostigmine increased sensory and motor anesthesia, but also delayed discharge time and was accompanied by 67% nausea and up to 50% vomiting. Lower doses did not show analgesic effect, but still had significant rates of side effects (nausea and vomiting).

N-methyl-D-aspartate (NMDA) receptor antagonists

Activation of NMDA receptors makes the neurons of the spinal cord more responsive to all types of input including pain stimuli (central sensitization). NMDA receptor antagonists, like ketamine, have shown analgesic activity. In fact in IV regional 0.1 mg/kg of ketamine is superior to clonidine (1 mcg/kg) in preventing tourniquet pain.

Errando in Spain showed that commercially available ketamine containing benzethonium chloride as a preservative is toxic in swine (Reg Anesth Pain Med 1999). Preservative-free solutions of ketamine have proven safe.

Hyaluronidase

It breaks down collagen bonds potentially facilitating the spread of local anesthetic through tissue planes. However, the evidence shows that at least in the epidural space it can decrease the quality of anesthesia. Its use seems limited to retrobulbar blocks.

Dextran

Dextran and other high-molecular-weight compounds have been advocated to increase the duration of local anesthetics. The evidence is lacking.

METABOLISM OF LOCAL ANESTHETICS

Ester local anesthetics

They are rapidly hydrolyzed at the ester linkage by plasma pseudocholinesterase, the same enzyme that hydrolyses acetylcholine and succinylcholine. The hydrolysis of 2-chloroprocaine is about four times faster than procaine, which in turn is hydrolyzed about four times faster than tetracaine. However, even tetracaine has a metabolic half-life of only 2.5-3.0 min (Tetzlatt, 2005).

In individuals with atypical plasma pseudocholinesterase the half-life of these drugs is prolonged and potentially could lead to plasma accumulation. Cerebrospinal fluid does not contain esterase enzymes, so if an ester is used for spinal anesthesia (e.g., tetracaine) its termination of action depends on absorption.

The hydrolysis of all ester local anesthetics leads to the formation of para-aminobenzoic acid (PABA), which is associated with a low potential for allergic reactions. Allergic reactions may also develop from the use of multiple dose vials of amide local anesthetics that contain methylparaben (PABA derivative) as a preservative.

As opposed to other ester type anesthetics, cocaine is partially metabolized in the liver and partially excreted unchanged in the urine.

Amide local anesthetics

They are transported into the liver before their biotransformation. The two major factors controlling the clearance of amide local anesthetics by the liver are hepatic blood flow and hepatic function. The metabolism of local anesthetics as well as that of many other drugs occurs in the liver by the cytochrome P-450 enzyme system. Because of the liver large metabolic capacity it is unlikely that drug interaction would affect the metabolism of local anesthetics. The rate of metabolism is agent specific (prilocaine > lidocaine > mepivacaine > ropivacaine > bupivacaine).

The metabolism of amide local anesthetics is relatively fast, although slower than esters. Elimination half-life for lidocaine is 1.5-2 h. Drugs such as general anesthetics, nor-epinephrine, cimetidine, propranolol and calcium channel blockers can decrease hepatic blood flow and potentially increase the elimination half-life of amides. Similarly, decreases in hepatic function caused by a lowering of body temperature, immaturity of the hepatic enzyme system in the fetus, or liver damage (e.g., cirrhosis) can lead to decreased rate of hepatic metabolism of the amides. Renal clearance of unchanged local anesthetic is a minor route of elimination (e.g., lidocaine is only 3% to 5% recovered unchanged in the urine of adults, while bupivacaine is 10% to 16%).

The primary metabolic pathway for mepivacaine is oxidation to 3-hydroxy and 4-hydroxymepivacaine. This pathway is less developed in neonates resulting in slower metabolism of mepivacaine in newborns than in adults (Raj's Regional Anesthesia).

The dibucaine number

People with atypical plasma pseudocholinesterase exhibit prolonged recovery after a dose of succinylcholine or mivacurium. Dibucaine is an amide local anesthetic that helps to identify those patients. Dibucaine binds strongly to **normal** plasma pseudocholinesterase inhibiting its action. This inhibition is reported as a number from 1to100 representing the percentage of normal enzyme inhibition. The larger the dibucaine number the larger the proportion of normal enzyme in existence.

- Dibucaine number of 80 or higher means that dibucaine is able to inhibit at least 80% of the enzyme and that the patient is a normal homozygous. A dose of succinylcholine in these patients will last 4-6 min.
- Dibucaine number of 50 means that the patient is heterozygous and that the effect of succinylcholine will be prolonged to up to 30 min.
- Dibucaine number of 20 is related to the homozygous atypical enzyme and the effect of succinylcholine could be expected to last up to 6 h. The incidence of the homozygous condition is 1:3,300.

LOCAL ANESTHETIC SYSTEMIC TOXICITY (LAST)

The capacity of a local anesthetic to produce systemic toxicity is directly related to plasma level of unbound drug. This plasma level depends on:

1. Total dose
2. Net absorption, which depends on: vasoactivity of the drug, site vascularity and use of a vasoconstrictor
3. Metabolism and elimination of the drug from the circulation

Brown et al reported a 1.2 in 10,000 incidence of systemic toxicity after epidural anesthesia and 19 in 10,000 after peripheral nerve blocks. Central nervous system (CNS) signs of toxicity usually precede cardiovascular (CV) manifestations. According to Mather et al, CNS and CV effects are "poorly correlated with arterial drug concentrations" and better correlated with the "respective regional venous drainage". According to them, lung uptake reduces the drug concentration by 40% and slower injection (3 min compared to 1 min) achieves similar decreases (Reg Anesth Pain Med, 2005).

Peak local anesthetic blood levels are directly related to the dose administered at any given site. However the vascularity of the site at similar doses is very important in determining different plasma levels. The absorption of local anesthetics from different sites is from highest to lowest: **endotracheal > intercostal > caudal > epidural > plexus blocks > sciatic/femoral > subcutaneous infiltration.**

Generally the administration of a 100-mg dose of lidocaine in the epidural or caudal space results in approximately a 1 mcg/mL peak blood level in an average adult. The same dose injected into less vascular areas (e.g., brachial plexus axillary approach or subcutaneous

infiltration) produces a peak blood level of app 0.5 mcg/mL. The same dose injected in the intercostal space produces a 1.5 mcg/mL plasma level.

Peak blood levels may also be affected by the rate of biotransformation and elimination. In general this is the case only for very actively metabolized drugs such as 2-chloroprocaine, which has a plasma half-life of about 45- 60 seconds.

For amide local anesthetics like lidocaine peak plasma levels after regional anesthesia primarily result from absorption **and usually occur within 1 h** (please see difference with tumescent anesthesia below).

Rodriguez et al studied 10 end-stage renal disease patients coming for A-V fistula (Eur J Anaesthesiol, 2001). The patients received an axillary block with a total of 650 mg of plain mepivacaine. Plasma levels were studied during 150 min. Peak levels of 8.28 mcg/mL (range 3.83-11.21) were obtained (normal 5 mcg/mL) within 60 min and decreased steadily thereafter. Patients did not exhibit signs of toxicity despite these high plasma levels.

This is in contrast with a case report by Tanoubi et al (Ann Fr Anesthe Reanim 2006), where an end-stage renal patient for A-V fistula received an axillary block with 375 mg (25 mL) of 1.5% mepivacaine and the patient presented with dysarthria, mental confusion and loss of consciousness without convulsions or arrhythmia. Mepivacaine plasma level at the time of symptoms was 5.1 mcg/mL.

Tumescent (diluted) anesthesia for liposuction

The use of highly diluted concentrations of lidocaine (0.1% or less) plus epinephrine (usually 1 mg per liter or 1:1,000,000) allows for painless and bloodless liposuction procedures. Lidocaine bounds to tissue proteins in this subdermal drug reservoir from where it is subsequently slowly released into the systemic circulation.

Diluted lidocaine and epinephrine-induced vasoconstriction, makes systemic uptake so slow as to match the liver maximum lidocaine clearance capacity of 250 mg/h. Therefore, according to De Jong, “the blood level remains below 5 mcg/mL toxic threshold, despite the administration of many times (e.g., 35 mg/kg) the conventional upper dose limit of undiluted full strength lidocaine” (Int J Cosmetic Surg 2002). **Peak plasma levels** of lidocaine using tumescent technique occur **between 5-17 hours** compared to less than 1 h for common infiltration.

Central nervous system toxicity

Toxic plasma levels are usually produced by inadvertent intravascular injection (Mather et al, Reg Anesth Pain Med, 2005) and are rarely the result of slow absorption from the injection site. This is the basis for incremental injection (pausing after 3-5 mL injection) and the use of vasoconstrictors. A sequence of symptoms tends to be biphasic with initial excitatory symptoms followed by depression of the CNS. These symptoms may include numbness of the tongue, lightheadedness, tinnitus, restlessness, tachycardia and convulsions followed then by unconsciousness, respiratory arrest and cardiac manifestations. The initial manifestations of CNS excitation culminating in seizures are the result of local anesthetic inhibitory effect on GABA-related pathways which is followed by effects both on GABA and NMDA receptors leading to an overall depression of the CNS and development of CV manifestations. There is no evidence that patients suffering from seizure disorders are at any increased risk for CNS local anesthetic toxicity, including seizures. The site of action for local anesthetic-induced seizures seems to be the amigdala, part of the limbic system, in the base of the brain.

Cardiovascular system toxicity

- The cardiovascular manifestations usually follow the CNS effects (therapeutic index). ***The exception is bupivacaine***, which can produce cardiac toxicity at sub convulsant concentrations. Bupivacaine cardiac toxicity was highlighted by Albright in an editorial published in Anesthesiology in 1979, in which he described several cases of refractory cardiac arrests in association with the use of bupivacaine.
- Rhythm and conduction are rarely affected by lidocaine, mepivacaine and tetracaine, but ***bupivacaine and etidocaine can produce ventricular arrhythmias.***
- EKG shows a prolongation of PR and widening of the QRS
- The incidence of CV toxicity with local anesthetics is higher in pregnancy due to higher proportion of unbound fraction.
- CV toxicity is increased under conditions of hypoxia and acidosis.

Maximum dose

While performing peripheral nerve blocks, anesthesiologists usually exceed what traditionally have been considered "maximum recommended doses" of local anesthetics. These recommended doses are in many cases the result of extrapolations from animal data that do not necessarily apply to our clinical practice. According to Rosenberg et al, the common recommendations for maximum doses, as suggested by the literature, "are not evidence based" (Reg Anesth Pain Med, 2004), and according to Mulroy have proven to be "poor approximation of safety" (Reg Anesth Pain Med, 2005).

It is known that peak plasma levels do not correlate with patient size or body weight in adults. Many practitioners have seen the need to reassess the subject of maximum doses of local anesthetics to better reflect the reality of clinical practice. As a result, the American Society of Regional Anesthesia ASRA convened a panel of experts, the "Conference in Local Anesthetic Toxicity" in 2001 to address this issue. Many papers related to that conference have been published. In a review article by Rosenberg et al (just cited) the authors argue that the safe doses instead should be block specific and related to patient's age (e.g., higher epidural spread in the elderly), organ dysfunction (especially for repeated doses) and whether the patient is pregnant. They suggest also adding epinephrine 2.5 to 5 mcg/mL, when not contraindicated.

In 2010 ASRA published the ASRA Practice Guidelines on Local Anesthetic Systemic Toxicity (LAST), which also includes some discussion on maximum doses. The practical advice is to use the lowest dose (concentration x volume) that is clinically effective. Dose reductions are particularly important in those patients considered at higher risk for LAST. That is patients younger than 4 months and older than 70 years, patients with cardiac conduction defects or history of cardiac ischemia. It is important to realize that neither body weight nor body mass index in adults correlates with plasma levels of local anesthetics. This correlation is more accurate in children. Block site, use of vasoconstrictor and patient related conditions such as cardiac, renal or hepatic are more important determinants of plasma levels of local anesthetics than body weight.

Toxic plasma concentration thresholds

The following are accepted plasma levels of selected local anesthetics, above which systemic effects are expected in humans:

Lidocaine 5 mcg/mL; mepivacaine 5 mcg/mL; bupivacaine 1.5 mcg/mL; ropivacaine 4 mcg/mL

Prevention of local anesthetic systemic toxicity

The best treatment for toxic reactions is **prevention.** Our recommendations are based on the most recent ASRA Practice Advisory on Local Anesthetic Toxicity, published in Regional Anesthesia and Pain Medicine Journal in 2010.

It is important to realize that when experts get together to develop practice guidelines they review whatever literature is available at the time and according to the strength of it they develop their recommendations. The types of recommendations and the level of evidence in which they are based follow the American Heart Association guidelines, available in their website and which I summarize as follows:

Type of Recommendation	
• Class I	Evidence or general agreement that a treatment or procedure is effective.
• Class II	Conflicting evidence or disagreement.
• IIa	Evidence mostly in favor.
• IIb	Usefulness is less established.
• Class III	Evidence/agreement that a treatment or procedure is ineffective and/or harmful.

Evidence Level	
• Level A	Randomized clinical trials.
• Level B	Non-randomized studies, some lab work data or multiple case reports and/or series.
• Level C	No other data than consensus opinion of experts.

As recognized in the ASRA 2010 guidelines, prevention is one of the most important factors when considering local anesthetic systemic toxicity (LAST). The following is a summary of the ASRA recommendations on Prevention of LAST:

- No single measure can prevent LAST
- Use the lowest clinically effective dose (volume x concentration) of local anesthetic. I; C
- Inject the local anesthetic incrementally in volumes of 3-5 mL, pausing for 15-30 sec. I; C
- Aspirate before injection (about 2% false negative). I; C

- Although imperfect, the use of epinephrine as an intravascular marker is recommended, with benefits outweighing risks in most patients. IIa; B
- The overall effectiveness of ultrasound in reducing the frequency of LAST is undetermined at this time. IIa; C

Treatment of local anesthetic systemic toxicity

When local anesthetic-induced seizures occur, hypoxia, hypercarbia and acidosis develop rapidly. ABC (Airway, Breathing and Circulation) is the mainstay of treatment. Administration of O_2 by mask, or ventilation support by bag and mask, is often all that is necessary to treat seizures. If seizures interfere with ventilation, benzodiazepines, small dose propofol or thiopental can be used. The use of succinylcholine effectively facilitates ventilation and, by abolishing muscular activity, decreases the severity of acidosis. However neuronal seizure activity is not inhibited and therefore, cerebral metabolism and oxygen requirements remain increased.

In an interesting study by Mayr et al, out of Innsbruck, Austria (Anesth Analg 2004), the authors induced cardiac arrest in 28 pigs by administering 5 mg/kg of 0.5% bupivacaine and stopping ventilation until asystole occurred. CPR was initiated after 1 min of cardiac arrest. After 2 min the animals received every 5 min either epinephrine alone; vasopressin alone; epinephrine plus vasopressin or placebo IV. In the vasopressin/epinephrine group all pigs survived and in the placebo group all pigs died. In the vasopressin alone 5 of 7 survived and in the epinephrine group 4 of 7 survived. This is in line with ACLS recommendations stating that one single dose of 40U of vasopressin IV can replace the first or second dose of epinephrine, although this is in contradiction with current 2010 ASRA guidelines for local anesthetic systemic toxicity treatment, which specifically recommends avoiding vasopressin (see LAST treatment recommendations below). The recommendation to avoid vasopressin in this setting seems to be based on an animal study by Di Gregorio et al (Crit Care Med, 2009) in which the authors showed that vasopressin was associated with poor hemodynamics and resulted in pulmonary hemorrhage in virtually all animals.

ACLS protocols must be followed with prompt and efficient airway management, defibrillation and use of vasopressors to support coronary perfusion as needed. Amiodarone should be favored over lidocaine to treat arrhythmias.

Lipid emulsion

In 2003, Weinberg and colleagues from the University of Illinois in Chicago reported the use of a 20% lipid emulsion in combination with cardiac massage to successfully treat bupivacaine-induced asystole in 9 out of 9 dogs. This led to the recommendation of using lipid emulsion to treat local anesthetics cardiovascular toxicity.

The original paper was accompanied by an editorial by Groban and Butterworth, who speculated that the most likely mechanism of action of lipid emulsion was that “in some way the lipid is serving to more rapidly remove LA molecules from whatever binding site serves to produce the cardiovascular depression that has come to be known as bupivacaine toxicity”.

In 2006 Rosenblatt et al published in Anesthesiology the first report of successful use of 20% lipid emulsion (Intralipid, Baxter Pharmaceuticals) in humans to treat local anesthetic systemic toxicity. This was the case of a 58-year old male in cardiac arrest after an interscalene block with bupivacaine. After 20 min of cardiac compressions and with the patient in asystole, a

bolus of 100 mL of Intralipid IV was given resulting in a reported "immediate" return of patient's rhythm. The lipid emulsion bolus was continued with an infusion of 0.5 mL/kg/min for 2 h. The patient was extubated 2.5 after hours after the arrest episode, without any apparent neurological sequelae.

After the initial report there had been numerous other reports in which lipid emulsion has been successfully used to treat local anesthetic systemic toxicity. It is now recommended to store lipid emulsion in all sites where local anesthetics are used. For more information on lipid emulsion and its use please visit www.lipidrescue.org.

It is important to emphasize that propofol has the same vehicle than Intralipid or other lipid emulsion solutions, but only half the concentration (10%). Using propofol to treat local anesthetic toxicity will not provide enough lipids, and through its active ingredient (di-isopropylphenol) will produce cardiac depression. Therefore, propofol is not indicated to treat local anesthetic-induced cardiac toxicity.

The following is a summary of the ASRA recommendations on Treatment of LAST:

- Prompt and effective airway management to prevent hypoxia and acidosis, known to potentiate LAST. I, B
- If seizures present, promptly administer a benzodiazepine. If not available use small doses of propofol or thiopental. Future data may support the use of lipid emulsion for treating seizures. I, B
- If seizures persist small doses of succiniylcholine should be considered to minimize acidosis and hypoxemia. I, C
- Although small doses of propofol can be useful in stopping seizures, larger doses depress cardiac function and should be avoided. III, B
- If cardiac arrest occur follow ACLS guidelines with the following modifications:
    - The use of small initial doses (10-100 mcg boluses) of epinephrine are preferred. IIa, C
    - Vasopressin is not recommended. III, B
    - Avoid calcium channel blockers and beta blockers. III, C
    - In ventricular arrhythmias prefer amiodarone. IIa, B
    - Treatment of ventricular arrhythmias with local anesthetics (lidocaine, procainamide) is not recommended. III, C
    - Use lipid emulsion at first signs of LAST after airway management. IIa, B
        - Give a bolus of 20% lipid emulsion 1.5 mL/kg (lean body mass)
        - Followed by 0.25 mL/kg/min infusion for at least 10 min after circulatory stability
        - If circulatory stability is not attained consider rebolusing and increasing your infusion to 0.5 mL/kg/min
        - Approximately 10 mL/kg of lipid emulsion in 30 min is recommended as the upper limit for initial dosing.
        - Propofol is not a substitute for lipid emulsion. III, C
        - Failure to respond to lipid emulsion and vasopressor therapy should prompt institution of cardiopulmonary bypass (CPB). IIa, B

When using amiodarone follow ACLS guidelines, 150 mg over 10 min, followed by 1 mg/min for 6 hrs then 0.5 mg/min. Supplementary infusion of 150 mg can be used as needed for up to 2 g. For pulseless VT or VF, initial administration is 300 mg rapid infusion in 20-30 mL of saline or dextrose in water.

Methemoglobinemia

Normal hemoglobin contains an iron molecule in the reduced or ferrous form (Fe^{2+}), the only form suitable for oxygen transport by hemoglobin. When hemoglobin is oxidized, the iron molecule is converted into the ferric state (Fe^{3+}) or methemoglobin. Methemoglobin lacks the electron that is needed to form a bond with oxygen and therefore it is incapable of oxygen transport. Because red blood cells are continuously exposed to various oxidant stresses, blood normally contains approximately 1% methemoglobin levels. Prilocaine and benzocaine can oxidize the ferrous form of the hemoglobin to the ferric form, creating methemoglobin. It is more frequently seen with nitrates like nitroglycerin. When MetHb exceeds 4 g/dL cyanosis can occur.

Prilocaine doses of more than 600 mg are needed to produce clinically significant methemoglobinemia. Depending on the degree, methemoglobinemia can lead to tissue hypoxia. The oxyHb curve shifts to the left (P50 < 27 mmHg). MetHb has a larger absorbance than Hb and 0_2Hb at 940 nm, but simulates Hb at 660 nm. In the presence of high MetHb concentrations the SaO_2 falsely approaches 85%, independent of the actual arterial oxygenation. Diagnosis needs clinical suspicion and confirmation by blood gas analysis.

Methemoglobinemia is easily treated by the administration of methylene blue (1-2mg/kg of a 1% solution over 5 min) or less successfully with ascorbic acid (2 mg/kg).

Chondrolysis after intrarticular continuous infusion of local anesthetics

In November 2009 the FDA issued a warning about the use of continuous intrarticular infusion of local anesthetics. The FDA reviewed 35 reports of chondrolysis (necrosis of articular cartilage) in otherwise healthy young patients given continuous intra articular infusions of local anesthetics using elastomeric pumps. Chondrolysis was diagnosed a median of 8.5 months after the infusion and in 97% of the cases involved the shoulder joint. The local anesthetics bupivacaine, chloroprocaine, lidocaine, mepivacaine, procaine, ropivacaine with or without epinephrine were used for 48-72 hrs. The FDA warns the practitioner that intra articular delivery is not an approved used of local anesthetics.

Allergy

True allergy (type I or IgE mediated) to local anesthetics is rare and presents within minutes after the exposure. It is relatively more frequent with esters, which are metabolized to para-amino-benzoic acid (PABA). PABA is frequently used in the pharmaceutical and cosmetic industries. Allergy to amide local anesthetics is exceedingly rare. There is no cross allergy between esters and amides. However use of methylparaben as a preservative in multidose vials can elicit allergy in patients allergic to PABA.

Delayed hypersensitivity reactions (type IV) are T-cell mediated and present 24 to 48 h after exposure. There are few cases in the literature of delayed hypersensitivity to lidocaine, but recent reports suggest it may be more frequent than previously reported. The North American Contact Dermatitis Group found that 0.7 % of patients who were patch tested in 2001-02 demonstrated delayed allergy to lidocaine (ASRA News, February 2006).

Eutectic mixture of local anesthetics (EMLA)

EMLA cream is a 1:1 mixture of 5% lidocaine and 5% prilocaine. One gram of EMLA contains 25 mg of lidocaine, 25 mg of prilocaine, an emulsifier, a thickener and distilled water. EMLA is a liquid at room temperature, containing up to 80% concentration of the uncharged base form of local anesthetic, which confers better dermal penetration. Anesthesia onset takes between 45 to 60 minutes. Its main use is in children. One or 2 grams of EMLA cream are applied per 10 cm^2 of skin and covered with an occlusive dressing (maximum application area 2000 cm^2 or 100 cm^2 in children less than 10 kg).

Drug interactions

Local anesthetics potentiate the effects of non-depolarizing muscle relaxants. Simultaneous administration of succinylcholine and ester local anesthetics, both metabolized by pseudocholinesterases, may potentiate the effect of each other. Cimetidine and propranolol decrease hepatic blood flow and amide local anesthetic clearance increasing the potential for systemic toxicity. Opioids and alpha-2 adrenergic agonists potentiate the effects of local anesthetics and vice versa.

Profile summary of selected local anesthetic agents

1. **Procaine:**
   Type: ester
Pka: 8.9

Protein biding: 5%

Characteristics: intermediate onset, low potency, short duration. Very short half-life (20 sec).

Other: it provides a short-duration spinal (potential benefit in outpatients).

2. **2-Chloroprocaine**:
Type: ester

Pka: 9.3

Protein binding: negligible

Characteristics: very fast onset despite high pka (ability to use higher concentrations could be the reason). Short duration (it has 30 minutes 2-segment regression in epidural). Very short half-life (30 sec).

Other: The original preparations contained sodium metabisulfite as a preservative. It was associated with serious neurological deficits when a large injection, planned for epidural, ended intrathecally. A second preservative, ethylenediamine tetra-acetic acid (EDTA) was associated with severe muscle spasms after epidural in ambulatory patients. EDTA chelates ionized calcium and this side effect may be secondary to action on paraspinal muscles.

The present solution is prepared without preservatives, and no back spasms have been reported.

3. **Tetracaine**:
Type: ester

Pka: 8.6

Protein binding: 85%

Characteristics: slow onset, high potency, long duration. Short plasma half-life (2.5 to 4 min).

Other: early experience with this product at high doses resulted in CNS toxicity, giving it a bad reputation, mostly undeserved. We still use it occasionally in our practice as lyophilized crystals dissolved in liquid mepivacaine for a final concentration of 0.2% tetracaine. It prolongs duration of surgical anesthesia in peripheral nerve blocks to 4-6 h. Tetracaine also is the drug that gets the longest prolongation from adding epinephrine to spinal anesthesia (up to 60% in the lumbar dermatomes).

4. **Cocaine**:
Type: ester

Pka: 8.6

Protein binding: very high

Characteristics: slow onset, short duration. Elimination half life 60-90 min. Urinary excretion of unchanged cocaine is usually less than 1%, but it can be up to 9% especially in acid urine. At the end of 4 hours, most of the drug is eliminated from the plasma. Cocaine metabolites (benzoylecgonine and ecgonine) may be present in the urine for 24-36 hours, but some metabolites may be identified for up to 144 h after administration (Ellenhom and Barceloux, 1988).

Other: It produces vasoconstriction while most of the local anesthetics, with the exception of ropivacaine, produce some degree of vasodilation. It interferes with the reuptake of cathecolamines, resulting in hypertension, tachycardia, arrhythmias and myocardial ischemia. It is used mainly for topical anesthesia of the nose. Doses below 100 mg (2.5 mL) are usually safe.

Cocaine can potentiate cathecolamine-induced arrhythmias by halothane, theophylline or antidepressants. Cocaine can induce coronary vasospasm and potential myocardial ischemia, without the need for coronary artery disease. Mixtures of lidocaine and phenylephrine are safer alternatives.

5. **Benzocaine**:
Type: ester

Pka 3.5

Characteristics: slow onset, short duration. It is the only LA with a secondary amine structure which limits its ability to pass through membranes (topical use only).

Other: Doses higher than 300 mg can induce methemoglobinemia.

6. **Lidocaine**:
Type: amide

Pka: 7.8

Protein binding: 65%

Characteristics: intermediate onset and duration, elimination half-life 45-60 min. Other: it is versatile (topical, infiltration, IV regional, neuraxial, antiarrhythmic) and widely used. Spinal use is associated with around 30% of TNS, especially with lithotomy position, knee arthroscopy and obesity. Lowering the concentration does not eliminate the problem with doses larger than 40 mg. Doses of 25-40 mg highly reduce the incidence of TNS.

7. **Mepivacaine**:
Type: amide

Pka: 7.6

Protein binding: 75%

Characteristics: intermediate onset and duration. Elimination half-life is 2-3 h in adults and 8-9 h in neonates.

Other: It produces less vasodilation than lidocaine. It has been used in spinal anesthesia. It has lower (but not zero) incidence of TNS.

> It is the agent we most commonly use for peripheral nerve blocks. A 1.5% of plain solution provides a short onset and dense surgical anesthesia lasting 2-3 h (3-4 h with 1:400,000 epinephrine). Prolonged postoperative analgesia, as with all other LA, is negligible after single-shot blocks.
> The primary oxidative metabolic pathway for mepivacaine is less developed in neonates resulting in slower metabolism of mepivacaine in newborns than in adults (Raj's Textbook of Regional Anesthesia).

8. **Bupivacaine**:
Type: amide

Pka: 8.1

Protein binding: 95%

Characteristics: high potency, slow onset, long duration. Elimination half-life 3-3.5 h in adults and around 8 h in neonates.

Other: lower concentrations (0.25% and less) produce analgesia with increased motor sparing (desirable in outpatients and obstetrics). Commercial bupivacaine is a 50:50 racemic mixture of the D (R) and L (S) enantiomers. Cardiac arrest associated with bupivacaine is difficult to treat possibly due to its high protein binding and high lipid solubility (please see toxicity).

9. **Ropivacaine**:
Type: amide

Pka: 8.2

Protein binding: 94%

Characteristics: onset and duration similar to bupivacaine, with slight lesser potency. Elimination half-life 1-3 h in adults.

Like bupivacaine, it is chemically related to mepivacaine, but as opposed to most local anesthetics, it is supplied as the pure L (S) enantiomer of the drug. The L (S) enantiomer is associated with less cardiac toxicity, intermediate between that of lidocaine and bupivacaine.

Other: It is a weak vasoconstrictor (only one other than cocaine). At lower concentrations (less than 0.5%) it may show a greater selectivity for sensory than motor blockade than bupivacaine.

10. **Levobupivacaine:**
Type: amide

Pka: 8.1

Protein binding: 97%

Characteristics: L (S) enantiomer of bupivacaine, very similar to ropivacaine.

Not available at this time in the United States.

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