Introduction

Local anesthetics (LA) represent a class of analgesic compounds that block trans-membrane sodium channels and reduce conduction safely in peripheral, spinal, and cortical axons [1–3]. Local anesthetics were first employed in South American cultures, where coco leaf poultices were found to provide effective topical analgesia when applied to wounds [1]. The active ingredient in coco leaf was later isolated by Albert Niemann in 1860 and named cocaine. Niemann noted that when tasted, small amounts of purified cocaine produced localized numbing of his tongue. In 1884 Carl Koller began using cocaine topically for ophthalmological surgery [1,2]. Since that time, a number of local anesthetics have been developed, utilized and abandoned. Ester-based LAs, including procaine, were first to be commercially developed and utilized in clinical practice. Amide LAs were developed later in the 1950s, the first being lidocaine.

Chemical structure

Local anesthetics all contain a lipophilic aromatic ring, hydrophilic tertiary amine and an ester or amide linkage. The general chemical structures of amide and ester anesthetics are illustrated in Figure 64.1. Local anesthetics are broadly classified either as “amide” or “ester” based on the nature of the linkage between the lipophilic aromatic ring and the hydrophilic amine. A simple way to distinguish an amide from an ester is the presence of an “i” in the name of the generic drug (excluding the -caine). For example, lidocaine is an amide, whereas tetracaine is an ester.

There are multiple agents which, when administered appropriately, have safe and effective anesthetic and analgesic effects. Local anesthetics are pharmacologically distinguished by differences in the aromatic ring and/or tertiary amine. Chemical groups attached to the aromatic ring influence speed of onset, while groups attached to the tertiary amine influence lipid/aqueous solubility and anesthetic potency.

Mode of action

In contrast to most drugs used in anesthesia and pain medicine, local anesthetics are only effective when deposited on or in the vicinity of the nerve fibers to be blocked. Local anesthetics act by reversibly interfering with both the initiation and propagation of neuronal action potentials (nerve impulses). They do this by decreasing or eliminating Na⁺ influx in the voltage-gated sodium channels at the nodes of Ranvier [2–4]. The result is an inability to raise axonal membrane potential to threshold and conduction blockade. Some local anesthetics (benzocaine, and biotoxins such as tetrodotoxin) physically block the Na⁺ channel. Most others diffuse through the axonal plasma membrane and bind to an internal receptor site located on the internal portion of the ion channel [2–5] (Figure 64.2). Local anesthetic binding results in configurational alterations in the ion channel that limit or prevent further Na⁺ conductance. Some local anesthetics (bupivacaine, ropivacaine) can also block the sodium channel directly by a process termed “frequency-dependent blockade”. These spindle-shaped amides can fit directly through the ion channel during axonal depolarization. Once they pass the channel they can directly bind to the receptor site and prevent further Na⁺ conductance. This process of selective neural blockade is highly efficient and effectively turns off those fibers that are firing most frequently. The ability to selectively block nerve fibers in proportion to their firing frequency underscores the clinical phenomenon termed differential blockade, whereby specific noxious fibers may be blocked to a greater extent than other sensory or motor fibers [2–5]. For example, low concentrations of bupivacaine and levo-bupivacaine block conduction in C fibers with greater selectivity than procaine and tetracaine, which are less effective.
at low concentrations and block all fiber types equally at high concentration. Differential block offers advantages in multiple settings, including the following:

(1) labor analgesia, where selective blockade of noxious fibers and sparing of sensory motor fibers may offer advantages;

(2) upper extremity block, where surgical pain is differentially blocked and perfusion is improved, while motor function is maintained;

(3) treatment of complex regional pain syndrome (CRPS), where autonomic fibers are preferentially blocked over motor fibers.

Other neuroanatomical factors responsible for differential block are discussed in sections that follow.

### Physiochemical correlates of local anesthetic activity

A number of LA physiochemical properties have been classically advocated to explain the pharmacokinetics of this class. In recent years a number of investigators have challenged these ideas [2,4,5] as being overly simplistic or incomplete explanations. Nevertheless, some degree of correlation between pKa, lipid solubility, and protein binding and onset/duration of LA effect have been described [3,4]. The pKa of a particular local anesthetic dictates its functionality and onset of activity. If the pKa is approximately physiological pH [4,7] the portion of drug in its uncharged form is nearly equiva-

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**Figure 64.1.** Chemical components of ester- and amide-based local anesthetics.

**Figure 64.2.** Local anesthetics can block sodium conductance and reduce conduction safety by two mechanisms. Most local anesthetics bind to a receptor located on the inner portion of the sodium channel and initiate a conformational change that closes the ion channel. Local anesthetics reach this site by diffusing across the axonal membrane. Highly charged local anesthetics have difficulty crossing this barrier although the charged moiety is able to bind the receptor more efficiently. Local anesthetics having a pKa close to physiological pH have 50% of drug ionized and 50% un-ionized. This optimal ratio allows enough uncharged molecules to pass through the membrane yet provides enough charged molecules to bind at the sodium channel receptor site. Some local anesthetics such as bupivacaine and ropivacaine are spindle-shaped and can penetrate the ion channel directly, but only when it opens during an action potential. These agents can rapidly reach and more efficiently bind to the receptor as they do not have to diffuse through the axonal membrane. This mechanism which allows actively firing nerve fibers to become selectively blocked in the presence of relatively low concentrations of LA is termed frequency-dependent neural blockade.
lent to the charged form. The drug is therefore less ionized and can more rapidly pass through the internodes or axonal membranes to reach its internal site of action \[3,4\]. This explains why the onset time of lidocaine (pKa \(= 7.6\)) is more rapid than bupivacaine (pKa \(= 8.5\)). Lidocaine's time to onset can be further reduced by the addition of bicarbonate. The low pKa of chloroprocaine also implies a slow onset; however, the higher concentration (3%) of drug solution can overcome this drawback, resulting in rapid onset of effect \[2,4\]. Localized infection decreases the tissue pH, which increases the number of charged molecules and often results decreased neural penetration. This may explain why LAs are less effective in infected and ischemic tissue.

Local anesthetic potency correlates with increasing lipid solubility, which is influenced by the polar groups attached to the tertiary amine. Like other anesthetics and analgesics, the more lipid-soluble the LA, the more potent it is. In other words, less drug is needed to achieve the desired anesthetic blockade. Highly lipid soluble LAs include tetracaine and bupivacaine, which have prolonged duration of activity \[2-4\].

Duration of activity has been related to the degree of protein binding of the local anesthetic, the concentration of the local anesthetic, and the addition of epinephrine to LAs that are intrinsic vasodilators (lidocaine, tetracaine). Drugs with high protein binding attach to intra-membrane proteins in axons, Schwann cells, and endoneurium and epineurium, to the extent that a reservoir of LA molecules remains sequestered at the site of deposition and is less likely to be removed by blood circulation in the vasa nervorum. This reservoir is able to maintain prolonged neural blockade by replacing LA that dissociates from the receptor site \[3\].

**Neuro-anatomical correlates of noxious blockade**

Certain aspects of neural anatomy and ultrastructure favor LA blockade of noxious impulses \[2-5\]. To reduce conduction effectively and safety in sensory and motor fibers, at least three myelin inter-nodes must be blocked. This “rule of three” favors blockade of thin unmyelinated fibers and also A-delta fibers which have small inter-nodal distances. Larger A-alpha and A-beta fibers are more resistant to blockade because of their size and large distance between nodes of Ranvier (Figure 64.3). Unmyelinated C fibers are easiest to block since LAs can impede Na⁺ conductance and action potential propagation at any single site along the course of the nerve fiber.

Additional factors which have significant impact on LA activity include the thickness of the peripheral or spinal nerve and its epineural and perineural coverings, as well as its microscopic anatomy. Increasing the concentration of a drug will speed its onset and intensity of blockade but may also increase its systemic toxicity. An exception is chloroprocaine, which has a very rapid onset due to its delivery concentration of up to 3%, and its ability to penetrate thick fibrous connective tissues making up the perineurium and epineurium. 2,4-Chloroprocaine is effective in eliminating a commonly observed L5–S1 root anesthetic window, as it can rapidly penetrate into this very thick mixed nerve and establish anesthetic conditions.

The microscopic anatomy of peripheral mixed nerves also has an influence on the fiber types that are blocked. It takes time for LA to diffuse through the nerve and a concentration gradient develops, whereby higher levels of drug occur at the peripheral site of deposition, and progressively lower levels accumulate in the central core. In general unmyelinated fibers and A-delta fibers are segregated to the outermost regions of the nerve (mantle) and are first to be blocked and last to recover. Motor and sensory fibers are located primarily in the core and tend to be more slowly and less effectively blocked, and are first to recover \[2-4\] (Figure 64.4). This finding as well as the above-described
“rule of three” help to explain the rapidity and increased intensity of blockade, and prolonged duration of LA effect on smaller-caliber noxious fibers, compared to sensory and motor fibers [2,4,5]. The usual sequence for differential blockade of various fiber types with low to increasing concentrations of local anesthetic is autonomic > noxious > cold > warm > light touch > deep touch > proprioception > motor fibers. In summary, LA blockade of proprioceptive and motor function occurs more slowly and often incompletely due to the greater degree of myelination, large intranodal distances, and core location of these fiber types.

**Metabolism**

Inactivation of the clinical effect occurs by diffusion away from the neuronal Na⁺ channels and by uptake into the vas nervorum and into the systemic circulation. It is here that metabolic inactivation of the linkage between the aromatic ring and tertiary amine can occur. The mechanism and site are very different for the amide and ester local anesthetics.

Ester linkages are metabolized primarily by pseudocholinesterase (plasma cholinesterase) and red blood cell esterases (minor). Hydrolysis occurs at the ester linkage, resulting in an alcohol and para-aminobenzoic acid (PABA) (or its derivatives). The formation of PABA is a major drawback of ester-linked LAs as it is responsible for mild to severe allergic reactions.

Amide linkages are metabolized in the liver by one of three pathways: aromatic hydroxylation, N,N-dealkylation, and amide hydrolysis.

Conditions which delay diffusion from the nerve fiber into the vasculature will prolong the duration of action of these drugs. The most common method to prolong LA duration is by the addition of a vasoconstrictors (epinephrine, clonidine) [6–8]. The microvasculature constricts resulting in a decreased blood flow and slowed drug uptake by the blood. Decreased uptake can also occur with hypothermia, hypotension and hypovolemia [3–5].

Site of injection is an important determinant in uptake and is dependent on tissue vascularity. The more vascular tissues have a faster drug uptake than less vascular tissue. Sites of injection with faster to slower uptake are noted as follows: intercostal > caudal > epidural > brachial plexus > femoral/sciatic > intrathecal.

**Indications**

Local anesthetics are used to locally anesthetize a wide range of specific body parts or areas to allow painless surgery. The application that first may be suggested for non-medical personnel is dental care, or perhaps minor laceration repair. Surgery can proceed distal to the site of local anesthetic placement. The locations include localized injection, peripheral nerve blocks as well as central nerve blockade. The only safe agents which can be utilized for intravenous regional anesthesia (Bier block) are lidocaine and prilocaine. Other typical indications are outlined in Table 64.1.

**Contraindications**

An allergic reaction to specific agents is an obvious contraindication. Allergy to para-aminobenzoic acid (PABA) is a contraindication to use of ester local anesthetics due to the fact that PABA is a metabolic product of ester metabolism. Methylparaben is a common preservative chemically similar to PABA and likewise can cause an allergic reaction. Metabisulfite is a commonly used preservative that may also cause allergic reactions but more notably is neurotoxic when used intrathecally. Local anesthetics containing any preservative should not be used intrathecally. Ester local...
Local anesthetics should be avoided in patients with atypical plasma cholinesterase due to slowed metabolism that can lead to enhanced local anesthetic toxicity. Total dosage must be monitored, with attention to avoiding the toxic dose and continuous monitoring of symptoms. The clinical symptomatology of lidocaine toxicity is presented in Table 64.2.

**Local anesthetic + opioid – additive analgesic**

There is an additive anesthetic effect when combining local anesthetics with opioid analgesics. There are well-documented spinal opioid receptors in the dorsal horn, and upregulation of opioid receptors has been described in chronically inflamed peripheral nerves.

The addition of morphine and fentanyl to intrathecal and epidurally administered local anesthetics decreases local anesthetic dose requirements while reducing surgical and post-operative pain intensity. One exception is chloroprocaine, which may antagonize epidural opioid analgesic effects.

**Dosages**

Correct dosing of LAs is primarily dependent on the particular agent and nerve or area to be injected. Descriptions of specific nerve blocks and appropriate LA dosages are described elsewhere. The onset duration and toxic doses of specific LAs are presented in Table 64.3.

**Advantages**

These agents reliably un-bind from their sites of action leaving no lasting effects. They are well tolerated and considered to be very safe when administered properly.

They are generally predictable regarding their individual onset times and durations of action. Varying the concentration and volume coupled with the addition of vasoconstrictors allows the duration and degree of blockade to be customized to whatever specific surgical or patient requirements present.

In the immediate post-operative period, patients can experience little to no pain, allowing for significant narcotic sparing, thereby minimizing narcotic-associated disadvantages.

Conduction blockade prior to incision can lessen the imprinting in the spinal cord of the nociceptive pathways thereby lessening the level of pain experienced over the next several days. The exact nature of this “wind-up” is being investigated.
Pre-incision conduction blockade can also decrease the incidence of developing a surgical site chronic pain syndrome.

These agents are available at low cost and can present significant cost savings, especially when considering the pharmacological costs of general anesthesia, shorter PACU times and less management time needed to address pain post-operatively. Additionally, some patients are able to be discharged sooner with fewer (immobility) complications such as deep venous thrombosis, ileus, and pulmonary atelectasis.

LAs may be combined neuraxially with opioids to gain additive analgesic benefits.

Esters are less cardiotoxic and neurotoxic than amides due to their rapid metabolism by plasma cholinesterase.

Amides offer several clinical advantages over esters, particularly fewer allergic reactions and easier titratability.

**Disadvantages**

These agents must be delivered directly to the desired nerve bundle. The delivery is often a problem due to technical issues accessing these anatomical sites, particularly cervical, brachial plexus, lumbar plexus, sciatic, and popliteal blocks. This is commonly the reason for inadequate neural blockade. There may be other issues precluding needle or catheter placement, such as patient cooperation, infection, or coagulation concerns.

All of these agents have some degree of neurotoxicity, which is dose and exposure duration dependent; particularly the amide agents.

Systemic dosage toxicity is related to several factors (Table 64.4). In addition to dosage and rapid vascular uptake, toxicity may also be metabolism-dependent. Rapidly metabolized agents such as chloroprocaine are less toxic. Agents (especially in a large dose) placed in highly vascular tissues are more rapidly absorbed by the blood which can quickly reach toxic levels, compared to less vascular tissues [8].

**Adverse events**

Situations which affect the level or efficacy of pseudocholinesterase can significantly alter the duration of action and toxicity of ester local anesthetics. This is more likely in premature infants, individuals with atypical pseudocholinesterase production or advanced liver disease.

Allergic reactions are very rare, but occur more commonly with the ester local anesthetics. This is probably due to the fact that a metabolic product from ester metabolism is PABA, a known allergen. Ester local anesthetics should therefore be avoided in known PABA-allergic patients. Other allergic reactions may be due to the preservative methylparaben, which is chemically similar to PABA.

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<tr>
<th>Table 64.3. Onset of action (infiltration)</th>
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<td>Onset (minutes)</td>
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<tr>
<td>Ester</td>
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<td>Chloroprocaine</td>
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<td>Tetracaine</td>
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<td>Benzocaine (topical)</td>
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<td>Amide</td>
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<td>Bupivacaine</td>
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<td>Ropivacaine</td>
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<tr>
<th>Table 64.4. Factors affecting systemic toxicity of local anesthetics</th>
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<tr>
<td>Site of injection</td>
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<tr>
<td>Dosage</td>
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<td>Vasoconstrictors</td>
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<td>Metabolism</td>
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Toxicity is a concern with either unintentional IV administration or rapid vascular uptake from tissue [8]. Some agents are reasonably benign such as lidocaine, prilocaine, or chloroprocaine, but others such as bupivacaine or tetracaine can result in seizures or fatal ventricular arrhythmias. Depending on the agent, dosage and injection location, treatment of toxicity may not be necessary. For example, symptoms may rapidly resolve without required treatment, such as lidocaine-associated dizziness or numb lips. Other agents may only require supportive care such as oxygen. Required supportive care may rapidly require airway and ventilatory support, seizure treatment, blood pressure support, and arrhythmia control. In cases of systemic toxicity due to bupivacaine, IV administration of a fat emulsion is effective [9]. Refer to Table 64.5.

Prilocaine can result in methemoglobinemia, when the total dose exceeds 600 mg.

Lidocaine and mepivacaine when given intrathecally have been associated with transient neurological syndrome, causing intrathecal nerve injury resulting in prolonged pain radiating to one or both legs. Although usually of short duration, it can last up to several months.

Chloroprocaine when administered intrathecally may result in prolonged sensory or motor deficits. This is most probably due to the bisulfate preservative and/or its very low pH.

Cauda equine syndrome is associated with intrathecal micro-catheters delivering a high concentration of lidocaine (and perhaps the preservatives). It consists of prolonged neural injury with motor weakness, significant pain and other sensory changes. These catheters are no longer in use.

Clinical presentation of systemic toxicity is variable, depending on the specific agent. Several agents are so rapidly metabolized that toxicity symptoms are very rarely seen, as with procaine and chloroprocaine. Different drugs present toxic symptoms in different sequence. For example, lidocaine first presents with dizziness or a numb tongue whereas bupivacaine may first present with seizures or fatal cardiac ventricular dysrhythmias.

Central nervous system symptoms are the most common type of toxic reaction to local anesthetics. Initial symptoms are excitatory (dizziness, visual, and auditory) followed by CNS depression such as unconsciousness, seizures, and coma.

### Table 64.5. Treatment of bupivacaine cardiac toxicity
- Fat emulsion 20% (Intralipid®)
- Bolus 1.5 mL/kg over 1 minute – may repeat 1x
- Infusion 0.25 mL/kg per min until stable

Maximum total 8 mL/kg

Cardiovascular toxicity initially presents as a dose-dependent depression of myocardial contractility and subsequently ventricular dysrhythmias.

### References