3. LOCAL ANESTHETICS

INTRODUCTION

Compared to general anesthesia with opioid-based perioperative pain management, regional anesthesia can provide benefits of superior pain control, improved patient satisfaction, decreased stress response to surgery, reduced operative and postoperative blood loss, diminished postoperative nausea and vomiting, and decreased logistic requirements. This chapter will review the most common local anesthetics and adjuncts used in the US military for the application of regional anesthetic techniques, with particular emphasis on medications used for peripheral nerve block (PNB) and continuous peripheral nerve block (CPNB).

BASIC REVIEW OF LOCAL ANESTHETICS

Local anesthetics are valued for the ability to prevent membrane depolarization of nerve cells. Local anesthetics prevent depolarization of nerve cells by binding to cell membrane sodium channels and inhibiting the passage of sodium ions. The sodium channel is most susceptible to local anesthetic binding in the open state, so frequently stimulated nerves tend to be more easily blocked. The ability of a given local anesthetic to block a nerve is related to the length of the nerve exposed, the diameter of the nerve, the presence of myelination, and the anesthetic used. Small or myelinated nerves are more easily blocked than large or unmyelinated nerves (Table 3-1). Myelinated nerves need to be blocked only at nodes of Ranvier (approximately three consecutive nodes) for successful prevention of further nerve depolarization, requiring a significantly smaller portion of these nerves to be exposed to the anesthetic. Differential blockade to achieve pain and temperature block (A-δ, C fibers) while minimizing motor block (A-α fibers) can be

TABLE 3-1

NERVE CLASSIFICATION AND SEQUENCE OF BLOCK WHEN EXPOSED TO LOCAL ANESTHETIC

Fiber Type	Myelin	Diameter (μm)	Function	Conduction Velocity	Time to Block
A-α	Yes	12–20	Somatic motor and proprioception	Fast	Slow
A-β	Yes	5–12	Light touch and pressure		
A-γ	Yes	3–6	Muscle spindle (stretch)		
A-δ	Yes	1–4	Pain (fast-localizing), temperature, firm touch		
B	Yes	1–3	Preganglionic autonomic		
C	No	0.3–1.3	Pain (nonlocalizing ache), temperature, touch, postganglionic autonomic	Slow	Fast
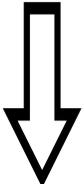
achieved by using certain local anesthetics and delivering specific concentrations to the nerve.

Local anesthetic structure is characterized by having both lipophilic and hydrophilic ends (ie, amphipathic molecules) connected by a hydrocarbon chain. The linkage between the hydrocarbon chain and the lipophilic aromatic ring classifies local anesthetics as being either an ester (–CO) local anesthetic, in which the link is metabolized in the serum by plasma cholinesterase, or an amide (–NHC) local anesthetic, in which the link is metabolized primarily in the liver.

The functional characteristics of local anesthetics are determined by the dissociation constant (pK_a), lipid solubility, and protein binding. The pK_a is the pH at which a solution of local anesthetic is in equilibrium, with half in the neutral base (salt) and half in the ionized state (cation). Most local anesthetics have a pK_a greater than 7.4. Because the neutral base form of the local anesthetic is more lipophilic, it can penetrate nerve membranes faster. As the pK_a of a local anesthetic rises, the percentage in the ionized

state increases and the onset of the block is slowed. Once the local anesthetic has passed through the cell membrane, it is exposed to the more acidic axioplasmic side of the nerve, favoring the ionized state. The ionized form of the molecule binds the sodium channel and blocks conduction.

The potency of local anesthetics is determined by lipid solubility. As lipid solubility increases, the ability of the local anesthetic molecule to penetrate connective tissue and cell membranes increases, causing the increase in potency.

The duration of action for local anesthetics is determined by protein binding. Local anesthetics with high affinity for protein binding remain bound to nerve membranes longer, resulting in an increased duration of action. Binding to serum α_1-acid glycoproteins and other proteins decreases the availability of free drug in the blood, reducing the potential for toxicity in the primary organs. The free fraction of local anesthetic in the blood is increased in conditions of acidosis or decreased serum protein, thus heightening the potential for toxicity.

LOCAL ANESTHETIC TOXICITY

Shortly after Carl Koller introduced cocaine for regional anesthesia of the eye in 1884 and physicians worldwide began injecting cocaine near peripheral nerves, reports of "cocaine poisoning" began appearing in the literature. Local anesthetics are indispensable to the successful practice of regional anesthesia, and physicians who use these techniques must be familiar with the signs and symptoms of local anesthetic toxicity. Initial excitatory symptoms of local anesthetic toxicity are manifestations of escalating drug concentration in the central nervous system, specifically the amygdala. Increasing local anesthetic concentration begins to block inhibitory pathways in the amygdala, resulting in unopposed excitatory neuron function. This process is manifested clinically as symptoms of muscular twitching, visual disturbance, tinnitus, light-headedness, or tongue and lip numbness. Extreme patient anxiety, screaming, or concerns about imminent death are also suggestive of toxicity. As the blood concentration of local anesthetic increases, these initial symptoms, without intervention, will progress to generalized tonic-clonic convulsions, coma, respiratory arrest, and death.

The cardiovascular system, though significantly more resistant to local anesthetic toxicity than the central nervous system, will exhibit arrhythmias and eventual collapse as local anesthetic concentrations increase. The relationship between the blood concentration of a particular local anesthetic that results in circulatory collapse and the concentration needed to cause convulsions is called the circulatory collapse ratio. As this ratio becomes smaller, the interval between convulsions and circulatory collapse decreases. Generally, this ratio tends to be small in the more potent, long-acting local anesthetics (bupivacaine and ropivacaine) compared with intermediate- and shorter-acting drugs (mepivacaine and lidocaine). The more potent a local anesthetic, the greater potential it has for causing cardiac depression and arrhythmias.

Local anesthetics have been shown to be myotoxic in vivo, although little evidence is available to determine this phenomenon's clinical relevance. Nevertheless, practitioners using local anesthetic for PNB or CPNB should consider the myotoxic potential of these medications in cases of unexplained skeletal muscle dysfunction. Local anesthetics have also been demonstrated to be neurotoxic in vitro, but the clinical significance of these findings remains theoretical.

A variety of anesthesia textbooks publish maximum recommended dosages for local anesthetics in an attempt to prevent high dose injections leading to toxicity. Because local anesthetic toxicity is related more to intravascular injection than to total dose, some physicians have suggested maximum dose recommendations are irrelevant. It is reasonable to assume that intravascular injections will occur, and practitioners of regional anesthesia should select techniques designed to minimize their occurrence, while maintaining preparation for appropriate treatments to use when such injections occur. The site of injection also affects the blood concentrations of local anesthetic. Blood absorption of local anesthetic varies at different injection sites according to the following continuum (from greatest to least absorption): intercostal > caudal > epidural > brachial plexus > femoral–sciatic > subcutaneous > intraarticular > spinal. Taking these factors into consideration, recommended techniques and conditions for local anesthetic injection are listed in Table 3-2.

Ropivacaine. Ropivacaine (Naropin, Abraxis BioScience Inc, Schaumburg, Ill) has a pK_a of 8.2. It is chemically similar to both mepivacaine and bupivacaine, but it is unique in being the first local anesthetic marketed as a pure levorotatory stereoisomer rather then a racemic mixture (ie, a combination of levorotatory and dextrorotatory molecules). Levorotatory enantiomers of local anesthetics are typically less toxic than dextrorotatory enantiomers. Because ropivacaine is less cardiotoxic than bupivacaine, it is the preferred long-acting local anesthetic for PNB anesthesia for many providers. The motor-block–sparing properties associated with ropivacaine spinal and epidural analgesia may provide an advantage over bupivacaine. Ropivacaine is considered the safest long-acting local anesthetic currently available, but it is not completely safe (cardiovascular collapse has been reported with its use), and all standard precautions should be observed with its use. Ropivacaine is the long-acting local anesthetic of choice at Walter Reed Army Medical Center because of its favorable safety profile and efficacy when used in a variety of regional anesthetics (Table 3-3).

Bupivacaine. Bupivacaine (Marcaine, Sensorcaine; both made by AstraZeneca, London, United Kingdom) has a pK_a of 8.1. With an extensive history of successful use, bupivacaine is the long-acting local anesthetic to which others are compared. Although a bupivacaine block is long acting, it also has the longest latency to onset of block. Bupivacaine is noted for having a propensity for sensory block over motor block (differential sensitivity) at low concentrations. These factors, as well as the low cost of bupivacaine compared to newer long-acting local anesthetics, have established bupivacaine as the long-acting local anesthetic of choice in many institutions. When long-duration analgesia is required, the use of bupivacaine for low-volume infiltration or spinal anesthesia is well established.

In spite of the popularity of bupivacaine for regional anesthesia, its use for large-volume techniques such as epidural or peripheral nerve anesthesia may be problematic; prolonged resuscitation following accidental intravascular injection has been reported. The recommended dosages of bupivacaine are the lowest of any of the amide local an-

esthetics. If patient safety were the only issue (other than cost, convenience, or availability) involved in long-acting local anesthetic selection, less toxic options would likely be used for large volume-blocks. This issue remains controversial.

Mepivacaine. Mepivacaine (Polocaine [Abraxis BioScience Inc, Schaumburg, Ill]; Carbocaine [AstraZeneca, London, United Kingdom]) has a pK_a of 7.6. In terms of function and toxicity, mepivacaine is often compared to lidocaine. In dogs, mepivacaine has been shown to be less cardiotoxic than lidocaine. Mepivacaine can be used for infiltration anesthesia with a similar onset to lidocaine but a longer duration. It is considered one of the least neurotoxic local anesthetics. In addition to low toxicity, mepivacaine has other properties that make it an attractive local anesthetic for intermediate-acting PNB, particularly in high-risk cardiac patients. Mepivacaine has excellent diffusion properties through tissue, allowing block success despite less than optimal needle position. It also produces intense motor block, which is desirable for a variety of surgical procedures such as shoulder surgery. Mepivacaine is the preferred local anesthetic to reestablish surgical block via preexisting CPNB catheters for patients requiring multiple operations. Low toxicity, rapid onset, and dense motor block make mepivacaine attractive for this application.

Lidocaine. With a low pK_a (7.7) and moderate water and lipid solubility, lidocaine or ligno-caine (Xylocaine [AstraZeneca, London, United Kingdom]) is the most versatile and widely used local anesthetic. Subcutaneous infiltration of lidocaine is the favored analgesic technique for many percutaneous procedures (such as venous cannulation). Despite a long history as the preferred agent for short-duration spinal anesthesia, in-trathecal lidocaine use has become controversial because of its association with transient neurologic

syndrome. Lidocaine 0.5% is the most common local anesthetic used for intravenous regional anes-thesia. Its low pK_a facilitates distribution of the local anesthetic into the exsanguinated extremity.

For use as an epidural anesthesia, lidocaine 2% is popular for cesarean sections and other major operations of the abdomen and lower extremities because of its low systemic toxicity, rapid onset, and intermediate length of duration. Lidocaine use for PNB has also been described; however, most physicians prefer longer acting local anesthetics for PNB, so that the duration of analgesia extends well into the postoperative recovery period.

REGIONAL ANESTHESIA ADJUNCTS AND ADDITIVES

The safe practice of regional anesthesia assumes an awake, though possibly sedated, patient who can manifest early signs and symptoms of evolving central nervous system or cardiovascular local anes-thetic toxicity. Moderate sedation is used by many practitioners to reduce the pain and anxiety that many patients perceive during regional anesthe-sia procedures. Although a variety of intravenous medications are available for sedation, midazolam, fentanyl, and propofol are common. Deep sedation or general anesthesia is avoided because patient indicators of pending local anesthetic toxicity or nerve injury are masked. Even moderate sedation with midazolam and fentanyl degrades detection of these patient indicators of injury. The anesthe-siologist must skillfully titrate sedation to strike a balance between patient comfort and safety during block placement.

The use of propofol and propofol with ketamine in the operating room following block placement for sedation is increasingly common. Ease of titration and rapid recovery with minimal side effects have popularized these medications for sedation complementing the regional block.

Remifentanil has also been successfully infused for regional anesthesia sedation and compares favorably with propofol.

Epinephrine (1:200,000 or 1:400,000) is one of the most common local anesthetic additives. It is combined with local anesthetics to produce regional vasoconstriction, resulting in block prolongation and reduced levels of local anesthetic in plasma. Epinephrine added to local anesthetics also serves as a marker of intravascular injection during single injection blocks. Accidental intravascular injection is indicated by observation of increased heart rate (≥ 10 beats/min), increased systolic blood pressure (≥ 15 mmHg), or decreased electrocardiogram T-wave amplitude (depression ≥ 25%), associated with as little as 10 to 15 μg of intravascular epinephrine. Epinephrine containing local anesthetic "test dose" injections via epidural and peripheral nerve catheters with gentle aspiration is an accepted method to protect against intravascular placement. Based on animal models, concerns that epinephrine containing local anesthetics may enhance ischemia following nerve injury or circulatory compromise have caused some physicians to reduce the dose of epinephrine (1:400,000) or limit its use to the test dose.

A plethora of local anesthetic additives have been used to enhance block duration and quality of analgesia. Multiple studies have shown the addition of opioids to intrathecal local anesthetics prolongs sensory anesthesia without prolonging recovery from ambulatory procedures. The combi-nation of local anesthetics with opioids for epidural anesthesia and analgesia is a common practice and has been shown to reduce local anesthetic require-ments in obstetric patients. Despite the recognition of opioid receptors outside of the central nervous system, the addition of opioids to peripheral nerve injections of local anesthetics has not been success-ful in improving PNB characteristics.

Clonidine, an α_2-adrenoceptor agonist that provides analgesia via a nonopioid receptor

mechanism, has been shown to be effective in prolonging analgesia in spinal, epidural, and peripheral nerve blocks. Clonidine 100 μg is frequently added to local anesthetic for PNBs at Walter Reed Army Medical Center to prolong analgesia. Dexamethasone 8 mg added to local anesthetics has also been reported to enhance the duration of sensory and motor blockade.

The list of medications used to improve regional anesthesia continues to grow, including drugs such as midazolam, tramadol, magnesium, neostigmine, and ketamine, as well as others that have had varying success. Expanding the list of local anesthetic drugs has the potential to improve patient safety, enhance analgesia, and expand the role of regional anesthesia in perioperative management.

TABLE 3-2

RECOMMENDED TECHNIQUES AND CONDITIONS TO MINIMIZE THE RISK OF LOCAL ANESTHETIC INTRAVASCULAR INJECTION

- Standard monitoring with audible oxygen saturation tone.

- Oxygen supplementation.

- Slow, incremental injection (5 mL every 10–15 seconds).

- Gentle aspiration for blood before injection and every 5 mL thereafter.

- Initial injection of local anesthetic test dose containing at least 5–15 μg epinephrine with observation for heart rate change > 10 beats/min, blood pressure changes > 15 mmHg, or lead II T-wave amplitude decrease of 25%.

- Pretreatment with benzodiazepines to increase the seizure threshold to local anesthetic toxicity.

- Patient either awake or sedated, but still able to maintain meaningful communication with the physician.

- Resuscitation equipment and medications readily available at all times.

- If seizures occur, patient care includes airway maintenance, supplemental oxygen, and termination of the seizure with propofol (25–50 mg) or thiopental (50 mg).

- Local anesthetic toxicity that leads to cardiovascular collapse should immediately be managed with prompt institution of advanced cardiac life support (ACLS) protocols.

- Intralipid (KabiVitrum Inc, Alameda, Calif) 20% 1 mL/kg every 3–5 minutes, up to 3 mL/kg, administered during ACLS for local anesthetic toxicity can be life saving. Follow this bolus with an Intralipid 20% infusion of 0.25 mL/kg/min for 2.5 hours.

TABLE 3-3

STANDARD ADULT ROPIVACAINE DOSAGES FOR SINGLE INJECTION AND CONTINUOUS REGIONAL ANESTHESIA AT WALTER REED ARMY MEDICAL CENTER

Regional Anesthesia Technique	Adult Single Injection*	Continuous Infusion of 0.2% Ropivacaine (mL/h)	Patient-Controlled Bolus Rate of 0.2% Ropivacaine[†] (mL bolus/20 min lockout)	Notes
Interscalene	30–40 mL of 0.5% ropivacaine	8–10	2–3	Often supplemented with an intercostal brachial nerve block
Supraclavicular	30–40 mL of 0.5% ropivacaine	8–10	2–3	Shortest latency block of the brachial plexus
Infraclavicular	35–40 mL of 0.5% ropivacaine	10–12	2–3	Catheter techniques less effective compared to supraclavicular catheters
Axillary	40 mL of 0.5% ropivacaine	10–12	2–3	Catheter techniques less common
Paravertebral	3–5 mL of 0.5% ropivacaine per level blocked	8–10	2–3	Catheters effective in thoracic region only
Lumbar plexus (posterior approach)	30–40 mL of 0.5% ropivacaine	8–10	2–3	Epidural spread is a concern
Femoral	20–30 mL of 0.5% ropivacaine	8–10	2–3	Catheter techniques may miss the obturator or lateral femoral cutaneous nerves
Sciatic (anterior or posterior approach)	20–30 mL of 0.5% ropivacaine	8–10	2–3	Proximal approaches to the sciatic nerve preferable for catheters
Sciatic (lateral or popliteal approach)	35–40 mL of 0.5% ropivacaine	10–12	2–3	Often the only approach available to the sciatic nerve following polytrauma
Lumbar plexus or femoral + sciatic	50–60 mL of 0.5% ropivacaine between both sites	5–10 for both catheters	2–3 on one catheter	Infusion rates divided between catheters based on distribution of patient's pain
Epidural	20–25 mL of 0.5% ropivacaine	6–10 thoracic 10–20 lumbar	2–3	Opioids often added to infusions
Spinal	5–15 mg of 1.0% ropivacaine	NA	NA	Opioids often added to injections

*Mepivacaine 1.5% can be used in place of ropivacaine at the volumes noted when a shorter duration block is desirable.
†Occasionally, a 5 mL bolus per 30-minute lockout is used in selected patients. Generally, total infusion (continuous plus bolus) > 20 mL/h are avoided.
NA: not applicable.