# Case 3

A 25-year-old, 75-kg man presents for open appendectomy. The surgery is performed under general anesthesia, without complications. After the specimen is removed, the attending surgeon leaves the operating room to dictate the operative report, leaving the intern and medical student to close the skin. Upon leaving, the surgeon asks them to "inject some local anesthetic into the wounds." The intern turns to you and asks which local anesthetic you suggest and how much to inject.

- What are the benefits of local anesthetic infiltration?
- What attributes are you looking for in a local anesthetic in this case?
- Which agent would you choose and what is the maximum dose?

# ANSWERS TO CASE 3:
# Local Anesthetic Infiltration

*Summary:* A 25-year-old healthy male undergoes uneventful laparoscopic appendectomy. Local anesthetic infiltration of surgical sites is requested.

- **Benefits of local anesthetic infiltration:** Decreased pain and narcotic usage
- **Local anesthetic attributes:** Long-acting, inexpensive, with addition of vasoconstrictor to decrease toxicity and in some cases increase duration
- **Agent of choice:** Bupivacaine with epinephrine, with a maximum dose of 225 mg bupivacaine

## ANALYSIS

### Objectives

1. Review pharmacology of local anesthetics.
2. Describe the various ways that local anesthetics can be used for surgical anesthesia.

### Considerations

For this application, a long-acting local anesthetic is injected, in an amount that is determined by the toxicity of the drug. As mentioned earlier, bupivacaine is chosen. Epinephrine is added in an attempt to prolong its action.

# APPROACH TO
# Local Anesthesia

Local anesthetic agents have been used for surgical anesthesia for over 100 years. The prototypical local anesthetic is cocaine, first incorporated into surgical practice in 1884 by Carl Koller for use in ophthalmic surgery. Cocaine has fallen out of favor as a primary local anesthetic because of its undesirable systemic effects and its abuse potential, but is still used today for otolaryngology cases where its topical anesthetic action and vasoconstriction capabilities are desirable.

Modern local anesthetics are used in a wide array of situations for surgery. Local anesthetics can be used as the sole anesthetic agent for abdominal and lower extremity procedures in the form of a neuraxial block technique (spinal anesthesia or epidural anesthesia). These techniques are overwhelmingly more common for obstetric anesthesia, and are also the technique of choice for joint replacement of the lower extremity in many anesthesia practices.

Local anesthetics have long been used as a part of a multimodal approach for postoperative pain control. Instillation of local anesthetic at the surgical site has commonly been used, but more recently, continuous infusions of local anesthetics in the forms of patient-controlled epidural anesthesia (PCEA) for thoracic and abdominal procedures as well as continuous peripheral nerve catheters are increasingly being used for postprocedural pain control and have been shown to decrease postoperative pain, as well as narcotic-associated morbidity. A thorough understanding of local anesthetics allows the anesthesiologist to tailor the correct drug, formulation, and technique to each clinical situation.

Historically, the maximal acceptable dose of local anesthetics, as well as adjuvants (such as opiates), have been based on a patient's weight. This practice is somewhat controversial since these different compounds are absorbed from different sites in the body at different rates. For example, the systemic absorption of local anesthetics is very high in vascular regions of the body such as the intercostal space for intercostals nerve blocks, but very low in the regions in which a sciatic nerve bloc is performed. To date, no studies have determined the actual "safe" doses of local anesthetics. However, if body weight is used to estimate the maximal safe dose, it seems more appropriate to base dosing on lean body weight rather than actual weight.

Local anesthetics are similar in their chemical structure and mechanism of action. These agents are amphipathic molecules consisting of three moieties: a lipophilic aromatic region (benzene ring), connected to a hydrophilic tertiary amide group, via an intermediate chain. Local anesthetics block neural transmission by blocking voltage-gated sodium ($Na^+$) channels. By binding to the $Na^+$ channel, the local anesthetic blocks $Na^+$ influx, thus abolishing membrane depolarization, action potential generation, and neural transmission.

Local anesthetics are weak bases, with pKa's ranging from 7.6 to 9.0. Therefore, both the ionic (protonated) and anionic forms are present at physiologic pH. However, only the nonanionic form can cross a cell's lipid bilayer and gain access to its site of action on the intracellular domain of the sodium channel protein. Because a low pH favors the ionized or ineffective form of the local anesthetic, its injection into an acidotic environment such as an abscess, will prove ineffective since the ion cannot enter the neuronal cells.

The anesthetic molecule preferentially binds to the open sodium channel; therefore, local anesthetics preferentially act upon rapidly-firing nerves, so-called "state-dependent blockade." This property is important when local anesthetics are used as antiarrhythmics to abolish ventricular tachycardia as they preferentially act on the rapidly depolarizing foci. As anesthetic agents, local anesthetics also show "state-dependent blockade," but other factors such as nerve diameter and degree of myelination predominate as determinants of nerve fiber blockade. Smaller, unmyelinated fibers are typically blocked before larger, myelinated ones. These properties explain the predictable sequence of nerve function blockade beginning with sympathetic fibers, progressing to pain and temperature fibers, followed by proprioception, then touch and pressure,

before finally, motor transmission impairment. The sequence of block resolution is the same, but regression is in reverse order.

**There are two classes of local anesthetics**: the esters, and the amides, based on its intermediate chain. The **esters,** such as procaine, benzocaine, and tetracaine, are more likely to cause an allergic reaction because of their cross reactivity to para-aminobenzoic acid (PABA). Metabolized by plasma esterase, ester anesthetics tend to have a shorter duration of action. The **amide local anesthetics**, such as lidocaine and bupivacaine, have an intermediate chain linkage that is an amide group. Amides undergo hepatic metabolism in the form of N-dealkylation followed by hydrolysis. Allergic reactions to amide anesthetics are rare.

Local anesthetic formulations are reported as percent solutions, or grams of material per 100 mL solution. Thus a 1% solution contains 1 g of material per 100 mL of solution, or 10 mg material per mL solution. Therefore, 0.5% bupivacaine contains 5 mg/mL, and a total of 45 mL would have to be infiltrated to reach the maximum dose of 225 mg.

## PHYSIOCHEMICAL PROPERTIES AND CLINICAL EFFECT

**Physiochemical properties** of local anesthetics predict their pharmacokinetic and pharmacologic properties.

### pKa

**An agent's pKa determines the onset of action.** The pKa is the pH at which a local anesthetic is present in both charged and uncharged forms in equal amounts. As mentioned earlier, only the anionic form of a local anesthetic can gain access to the binding site on the sodium channel, which is located on the intracellular portion of the protein. Local anesthetics with a pKa closer to 7.4 will have a greater percentage of molecules in the anionic form compared to those with higher pKa's, and therefore will have a quicker onset of action. The notable exceptions to this rule are procaine and chloroprocaine both of which have a high pKa but very rapid onset of action.

### Lipid Solubility

**Lipid solubility is directly correlated with potency.** More lipophilic agents more easily cross the lipid bilayer and become pharmacodynamically active.

### Protein Binding

**The degree of protein binding is a primary determinant of duration of action for local anesthetics.** The higher the degree of protein binding, the longer it engages the sodium channel, and longer is its duration of action. Protein binding in the serum is most commonly to $\alpha_1$-acid glycoprotein and

albumin, which leads to sequestration of the local anesthetic and prevents it from being metabolized, extending its plasma half-life.

In addition to the physiochemical properties, other factors affect the properties of neural blockade.

## Dose

**The higher the dose, the faster the onset of action and the longer the duration of neural blockade.**

## Site of Injection

Common sites of local anesthetic injection vary in degrees of vascularity leading to differing pharmacokinetics of these injections. **The more vascular the area of injection, the higher the peak plasma level of local anesthetic, the higher the potential for toxicity, and the shorter the duration of blockade.** The peak plasma levels of local anesthetic depending on site of injection are in descending order: intravenous, intercostal, caudal, epidural, upper extremity (brachial plexus), lower extremity (sciatic/femoral).

## Anesthetic Adjuvants

Addition of adjuvant drugs can favorably affect the pharmacokinetics and pharmacodynamics of local anesthetics.

## Sodium Bicarbonate

Most local anesthetic formulations are prepared with a pH of 4 to 6; as a result, most of the molecules are present in the poorly lipid-soluble ionic form. **The addition of sodium bicarbonate to local anesthetic preparations raises the pH of the solution and increases the percentage of anionic local anesthetic molecules, and thus speeds the onset of action.** There is also data to suggest that by increasing the pH, the addition of sodium bicarbonate decreases the pain of injection.

## Epinephrine

The addition of epinephrine to local anesthetic solutions has a myriad of benefits. **One of the most useful applications of epinephrine-containing preparations compared to plain solutions is the ability to rapidly detect an intravascular—specifically an intra-arterial—injection.** Even relatively small amounts of local anesthetic, if injected directly into the vasculature can lead to toxicity (see Case 15). If a local anesthetic containing epinephrine is injected into a blood vessel, a 10% to 20% increase in heart rate and/or blood pressure will result. Thus it is a common practice to include epinephrine in the small or "test" dose which precedes the injection of any large amount of

**Table 3–1 PROPERTIES OF COMMONLY USED LOCAL ANESTHETICS**

| DRUG | CLASS | pKa | POTENCY | ONSET OF ACTION | DURATION OF ACTION | MAXIMUM DOSE (PLAIN) | MAXIMUM DOSE (EPINEPHRINE ADDED) |
|---|---|---|---|---|---|---|---|
| 2-Chloroprocaine | Ester | 8.7 | Low | Very Rapid | Short | 800 mg | 1,000 mg |
| Procaine | Ester | 8.9 | Very low | Rapid | Short | 400 mg | 600 mg |
| Tetracaine | Ester | 8.5 | High | Slow | Very long | 100 mg | 200 mg |
| Lidocaine | Amide | 7.72 | Moderate | Rapid | Moderate | 300 mg | 500 mg |
| Mepivacaine | Amide | 7.7 | Moderate | Moderate | Moderate | 400 mg | 550 mg |
| Ropivacaine | Amide | 8.1 | High | Slow | Long | 225 mg | 225 mg |
| Bupivacaine | Amide | 8.1 | High | Slow | Very Long | 175 mg | 225 mg |

local anesthetic. If a rise in heart rate and/or blood pressure is observed, the injection should be halted and the needle/catheter repositioned before continuing. The addition of epinephrine to the test dose lends an increased sensitivity to intravascular injection when compared to aspiration before injection.

**The addition of epinephrine to local anesthetics also leads to local vasoconstriction, less systemic uptake of the local anesthetic, and a decreased risk of toxicity.** The duration of action of long-acting agents such as bupivacaine are not affected by the addition of epinephrine. However, the decreased systemic absorption can extend the clinical effect of shorter acting agents such as lidocaine and chloroprocaine.

Epinephrine can also potentiate the analgesic action of local anesthetics through alpha-2 receptor-mediated action.

## Comprehension Questions

3.1. A 48-year-old woman presents for laparoscopic cholecystectomy. Her past medical history is significant only for prior tonsillectomy and adenoidectomy as a child. She states that she has an allergy to local anesthetics. Upon further questioning, she states that she received Novocain (procaine) at the dentist and her "heart began to race and she became light-headed." Which of the following conditions most likey explains this patient's reaction?

A. A true allergic reaction to the amide local anesthetic procaine
B. An allergic reaction to a breakdown product of procaine
C. A side effect of epinephrine, which was added to the Novocain preparation
D. A somatization of the patient's apprehension toward dental procedures
E. A side effect of phenylephrine, which was added to the Novocain preparation

3.2. A 60-kg 17-year-old man presents for open reduction and internal fixation of an ankle fracture. You discuss a general anesthetic for intraoperative management with a sciatic block via the popliteal approach. You decide to use 20 mL of 0.5% bupivacaine with 1:200,000 of epinephrine. How many mL of 1:1000 epinephrine should you add to your bupivacaine to reach the appropriate concentration?

A. 0.05 mL
B. 0.1 mL
C. 0.02 mL
D. 0.2 mL
E. 0.04 mL

## ANSWERS

3.1. **C.** The patient's reaction is most likely a representation of the side effects of epinephrine that is often added to local anesthetic preparations in order to increase duration of action and reduce systemic absorption of the local anesthetic. The patient's symptoms of tachycardia are more consistent with the sympathetic sequelae from epinephrine injection rather than a true allergic reaction (bronchospasm and urticaria). Procaine is an ester local anesthetic, which is more likely to cause an allergic reaction than amide local anesthetics, although the incidence of ester-mediated allergic reaction is very rare. Ester local anesthetics are broken down to para-aminobenzoic acid (PABA), a known allergen. Further, certain preservatives in local anesthetics such as methylparaben and sulfites can cause an allergic response.

3.2. **B.** A 1:1000 solution of epinephrine contains 1 mg/mL epinephrine. Twenty mL of 1:200,000 solution would contain 100 μg of epinephrine (1 g epinephrine/200,000 mL × 20 mL = 0.0001 g or 100 μg, or 0.1 mg). To add 100 μg epinephrine, one would need to add 0.1 mL of 1:1000 epinephrine (100 μg × 1 mg/1000 μg × 1 mL/ 1 mg = 0.1 mL).

### Clinical Pearls

- Local anesthetics will not work in acidotic tissues.
- Factors determining the onset, duration, and potential complications of a regional block with local anesthetics include the site of injection, the dose of local anesthetics, the volume of the local anesthetic, and its physiochemical properties.
- The addition of epinephrine to local anesthetics is useful to detect intravascular injection, to increase duration of the blockade, and to prevent systemic absorption and toxicity.

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