



## CE

## Article #3 (1.5 contact hours)

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## KEY FACTS

- Local anesthetic agents can be used effectively in managing postoperative pain while minimizing the undesired systemic effects of traditional systemic analgesics.
- Drugs or drug delivery systems that produce uninterrupted and prolonged analgesic effects are more likely to be effective in preventing secondary hyperalgesia and the development of chronic pain states.
- A variety of novel local anesthetic delivery systems are currently available, including constant-rate delivery catheters, implantable pumps, and transdermal creams and patches.

# Local Anesthetics: Pharmacology and Novel Applications

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**ABSTRACT:** The advent of novel drug delivery systems has allowed local anesthetics to become a popular and practical means of providing analgesia with minimal systemic effects. Through the complete and continuous blockade of pain transmission, these drugs can be effectively used to reduce or prevent the development of secondary hyperalgesia. Currently used novel drug delivery systems for local anesthetics include ambulatory electronic delivery, patient-controlled infusion, implantable local infusion, and ambulatory elastomeric infusion. Topical application products include transdermal creams and patches as well as iontophoretic delivery systems.

The timely identification and treatment of pain help to reduce its negative effects on patient health and well-being. Furthermore, it has become increasingly apparent that the detrimental consequences of pain on patient health outweigh the potential negative effects of treating pain. Pain produces stress, which can lead to compensatory elevations in adrenocorticotrophic hormone, cortisol, antidiuretic hormone, catecholamines, aldosterone, renin, angiotensin II, and glucose.<sup>1,2</sup> When severe, stress can lead to cardiorespiratory compromise, catabolism, and immunosuppression.<sup>1,2</sup> Increases in sympathetic nervous system activity can decrease bowel motility and gastrointestinal blood flow, resulting in bacterial overgrowth and increased potential for ischemia and translocation of harmful bacteria.<sup>1</sup>

An effective plan for managing surgical pain must incorporate the patient's past and current health status; age; past, present, and anticipated sensitivity to pain; and drug effects, including potential drug interactions. Inadequate or inappropriate pain therapy results in pain that is more difficult to treat, often resulting in the need for prolonged or more frequent administration of systemic analgesics, which, in turn, results in increased cost, prolonged hospitalization, and the potential for systemic side effects and toxicity.<sup>2,3</sup>

Local anesthetics have a long history of providing pain relief from a variety of medical and surgical procedures.<sup>1</sup> Although primarily limited to topical, local, or regional (epidural) administration, new topical formulations and the advent of

novel drug delivery systems have markedly increased both the acceptance and clinical utility of local anesthetics. Local anesthetics are comparatively inexpensive, effective, and safe compared with traditional analgesic treatments. Most traditional analgesic drugs, including opioids and  $\alpha_2$ -agonists, have a short duration of action and the potential to produce systemic side effects, including emesis, respiratory depression, drowsiness, and ileus.<sup>3,4</sup> This article focuses on newer therapeutic modalities for administering local anesthetic drugs in veterinary patients. The routine use of local anesthetics for wound lavage, direct nerve block, or to produce intracavitary, intraarticular, and epidural analgesia is described elsewhere.<sup>3-6</sup>

## BACKGROUND

Pain can be either physiologic or pathologic.<sup>2,7</sup> Physiologic pain is produced by acute, transient, non-tissue damaging stimuli and is protective, evoking either defensive or escape behaviors in most animals. Activation of specialized receptors located on bare nerve endings produces pain. These receptors transform noxious stimuli into action potentials (electrical signals) that are transmitted by thinly myelinated (A $\delta$ ) and unmyelinated (C) nerve fibers to the dorsal horn of the spinal cord where they activate additional receptors on nerves that connect locally, project to the brain, or activate rapidly conducting myelinated nerves (A $\beta$ ) in the ventral horn of the spinal cord.<sup>2,7</sup> Activation of these receptors results in the rapid removal of the affected body part from the source of the noxious stimulus.

Pathologic pain is caused by tissue or nerve damage.<sup>2,7</sup> Trauma and surgery cause pain by damaging skin, muscles, and small nerve endings. Inflammation and flare formation at the site of injury are common signs of tissue injury. The magnitude and severity of the initiating injury determines the extent of the injured area and the potential for two types of hyperalgesia to develop. Primary hyperalgesia is initiated by the local release of chemicals (e.g., prostaglandins, histamine, nerve growth factor) that sensitize nerves at the site of injury to both mechanical and thermal stimuli (Figure 1). More severe injuries produce a sustained input of electrical signals to the dorsal horn that activates and unmasks additional dorsal horn receptors and signaling cascades that amplify input, resulting in central sensitization. Central sensitization is responsible for the development of hyperalgesia outside the injured area<sup>2,7</sup> (secondary hyperalgesia; Figure 1).

Considerable evidence suggests that surgical pain can be reduced by administering drugs before (preemptive) surgery.<sup>2,7-9</sup> Administering local anesthetics (e.g., lidocaine, bupivacaine, ropivacaine) before surgery can block the activation of pain-transmitting neurons and prevents

the development of central sensitization. Several studies in humans and rats also suggest that surgical pain can be equivalently treated by administering local anesthetics (e.g., lidocaine) after surgery.<sup>8,9</sup> These same studies also demonstrate that for postsurgical treatment to be effective, treatment should focus on the continuous blockade of peripheral sensory nerve pathways.<sup>8</sup> Together, these studies suggest that drugs or drug delivery systems that produce uninterrupted and prolonged analgesic effects are more likely to be effective in preventing secondary hyperalgesia and the development of chronic pain states.<sup>7-9</sup>

## HISTORY AND PHARMACOLOGY

The first known application of a local anesthetic in veterinary medicine was in 1885 by McLean, a veterinarian in Meadville, Pennsylvania.<sup>10</sup> McLean administered cocaine hydrochloride as a local nerve block for diagnosing equine lameness. This same year, Corning injected cocaine intrathecally in a dog to provide spinal analgesia.<sup>10</sup> Approximately 15 years later, this same technique became popular in human medicine. Cocaine's less desirable properties—toxicity and addiction—became apparent in the early 1900s. This discovery prompted the development of safer alternative local anesthetic drugs (e.g., procaine, lidocaine). Einhorn (1905) developed procaine, and Lofgren (1944) synthesized today's most popular local anesthetic, lidocaine, which quickly became popular in dental and surgical procedures for local infiltration and nerve blockade.<sup>10</sup> Subsequently, more than 50 synthetic local anesthetic drugs have been developed for a variety of clinical applications.

Local anesthetics inhibit the conduction of nerve impulses generated by noxious and innocuous stimuli.<sup>11</sup> They produce this effect by blocking pores or channels in the membrane of nerve cells, thereby inhibiting entry of sodium ions into the cell, subsequent depolarization, and production of an electrical signal.<sup>4,10,11</sup> Sensations typically disappear in the following order: pain, cold, warmth, touch, and deep pressure; they return in the reverse order.<sup>4,10,11</sup> Additional (and, at times, controversial) benefits of local anesthetic (particularly lidocaine) administration include potent antimicrobial effects, reduction in local inflammatory mediators, reduction in ischemia-reperfusion injury, improved wound healing, the absence of tissue damage/irritation, lack of hypersensitivity, and rapid penetration.<sup>10,12-16</sup>

Local anesthetics generally consist of three basic units: an unsaturated aromatic group (benzene ring), an intermediate chain, and a tertiary amine ring. The aromatic ring structure affects the lipophilicity and potency of each compound (the more lipid solubility there is, the greater the potency of the drug).<sup>10,11,17</sup> Typi-

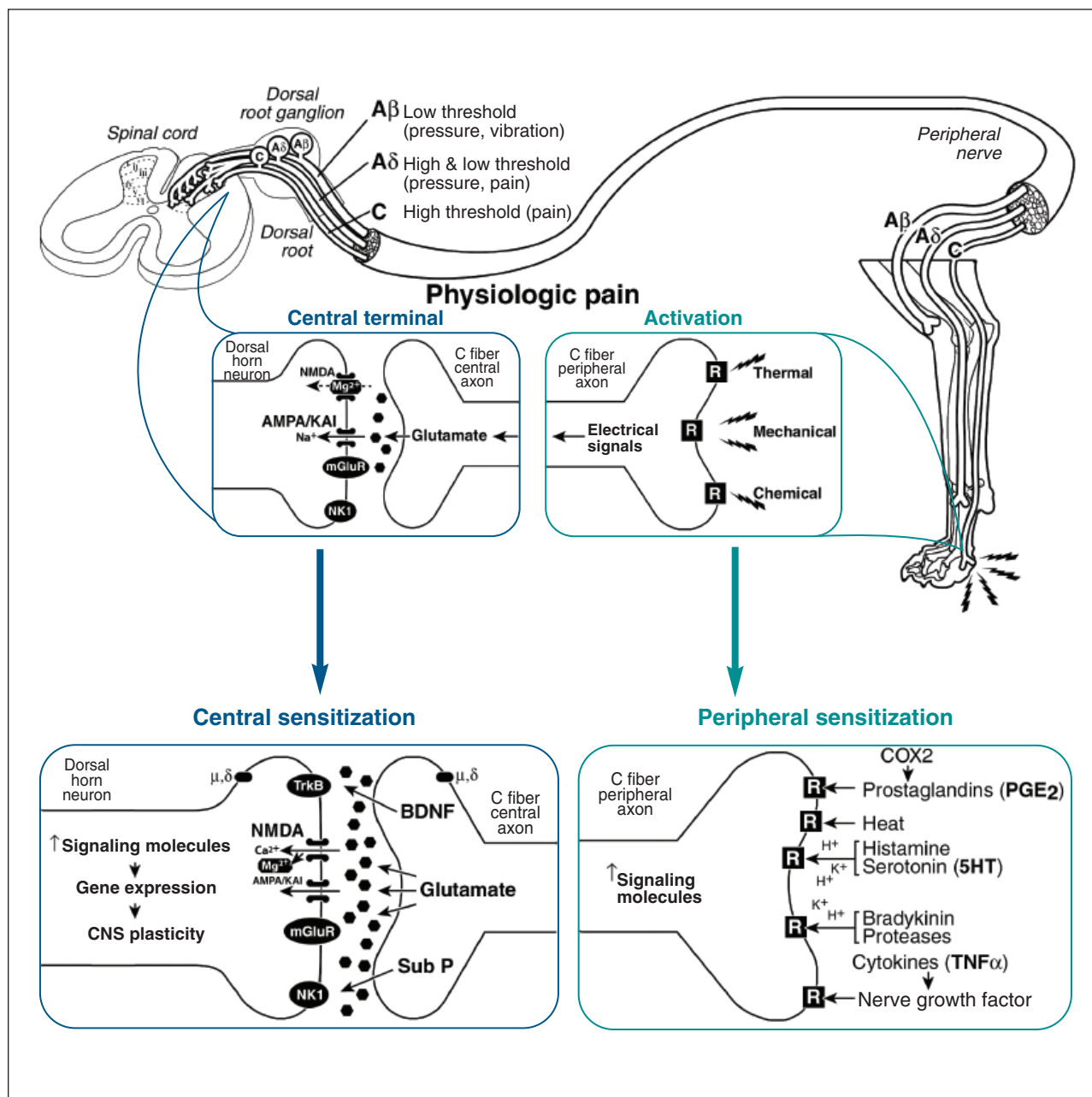
cally, the smaller, lipophilic molecules have a faster onset of action.<sup>10,11,17</sup> The composition of the intermediate chain classifies local anesthetics as either ester- or amide-linked.<sup>10,11,17</sup> The most common aminoesters are procaine, chlorprocaine, and tetracaine, whereas the most common aminoamides are lidocaine, mepivacaine, bupivacaine, and ropivacaine (Table 1). Ester-linked local anesthetics are hydrolyzed in plasma, whereas amides are metabolized in the liver.<sup>10,11,17</sup> The para-aminobenzoic acid byproduct of ester hydrolysis is responsible for allergic responses in humans.<sup>10,11</sup> Because amide breakdown results in a somewhat different spectrum of metabolites in dogs and cats than in humans, allergic reactions are rare.<sup>10,11</sup> Hepatic degradation of the amide class requires conjugation with glucuronic acid.<sup>10</sup> Therefore, because of cats' decreased capacity to glucuronidate drugs, they are more likely than dogs to develop toxic side effects.<sup>10</sup> Final elimination of metabolites depends on the renal mechanisms. The tertiary amine determines the  $pK_a$  of the local anesthetic and the amount of uncharged base available for penetration through membranes (the more base there is, the more rapid the onset and greater the potency).<sup>10,17</sup> Protein binding limits drug availability and prolongs the duration of action.<sup>10,11</sup> The addition of vasoconstrictors, such as epinephrine, to a local anesthetic solution delays the rate of vascular absorption and prolongs the duration of action.<sup>10,18</sup> The addition of bicarbonate to the local anesthetic solution speeds the onset of drug effect but shortens the duration of action because more drug is available in base form.<sup>10</sup> The combination of lidocaine and bupivacaine has been promoted for clinical use to hasten the onset of action and prolong the local anesthetic effect.<sup>11</sup>

Side effects of local anesthetics are rare if appropriate dosage recommendations are adhered to and are most common in association with deliberate or inadvertent IV delivery. Central nervous system and cardiovascular disturbances are the most common side effects reported.<sup>4,10,18-20</sup> Humans often report a metallic taste, restlessness, and difficulty focusing.<sup>10</sup> This often progresses to slurred speech and seizures if allowed to continue (Table 1).<sup>10</sup> The most common central nervous system effects in dogs include sedation, nausea, ataxia, nystagmus, and muscle tremors.<sup>18-20</sup> Cardiovascular effects usually occur subsequent to central nervous system effects and can be both electrical and mechanical. Specifically, the rate of depolarization of individual cardiac cells is reduced, leading to prolonged conduction of the cardiac impulse, arrhythmias, or bradycardia and asystole.<sup>4,18-20</sup> Rapid IV administration of local anesthetics can decrease vascular tone and myocardial contractility, resulting in the acute onset of hypotension.<sup>4,10,18-20</sup> More potent local anesthetics (bupivacaine) have a greater effect on cardiac contractility.<sup>10</sup> Methemoglobinemia has also been reported, particularly with topical prilocaine and benzocaine.<sup>10,18-20</sup> It is believed that the formation of methemoglobin is due in part to oxidative damage from the breakdown products of local anesthetic metabolism.<sup>10,18-20</sup> Such agents should be used with caution, particularly in species most susceptible to oxidative injury (e.g., cats).

## NOVEL CLINICAL APPLICATIONS AND DELIVERY SYSTEMS

The administration of bolus and continuous local infusions of local anesthetic drugs has gained popularity in human medicine (Table 2). These delivery systems are very versatile, allowing delivery of local analgesics, chemotherapeutics, and antibiotics in ambulatory patients. Successful use of these analgesic systems has been associated with decreased use of supplemental systemic analgesics, shortened hospital stays, and overall decreased patient morbidity.<sup>21</sup> Motor blockade has been minimal, and there has been no reported

*(text continues on page 923)*



**Figure 1**—Physiologic or nociceptive pain caused by thermal, mechanical, or chemical stimuli serves as a warning or alarm system in response to impending tissue damage. Nociceptive pain is activated by noxious stimuli acting on high threshold sensory ( $A\delta$  and  $C$ ) nerve fiber terminals located in peripheral tissues. The resultant electrical signal generated causes the release of glutamate in central nerve terminals in the spinal cord. Glutamate activates  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate (KAI) receptors, causing a transient localized sensation. The release of local tissue enzymes (cyclooxygenase 2 [COX2]) and inflammatory substances, including prostaglandins, histamine, serotonin, bradykinin, proteases, cytokines, and nerve growth factor, produces peripheral sensitization and primary hyperalgesia at the site of injury and pain in response to innocuous low-intensity stimuli. More intense noxious stimuli caused by extensive tissue or nerve damage activate  $N$ -methyl-D-aspartate (NMDA), metabotropic glutamate ( $mGluR$ ), neurokinin-1 ( $NK1$ ), and tyrosine kinase B ( $TrkB$ ) receptors in dorsal horn neurons, resulting in central sensitization. Central sensitization is characterized by secondary hyperalgesia and allodynia (i.e., prolonged and amplified response to noxious and innocuous stimuli at and around the site of injury) and is an activity-dependent increase in dorsal horn nerve excitability. (BDNF = brain-derived neurotrophic factor;  $Ca^{2+}$  = calcium; CNS = central nervous system;  $Mg^{2+}$  = magnesium; TNF = tumor necrosis factor)

Table 1. Characteristics of Commonly Used Local Analgesics

| Generic Name | Trade Name and Approximate Cost/ml             | Chemical Name                                                  | Percentage Solution <sup>a</sup>                                                             | Potency Ratio (Procaine = 1) | Stability                                                                                                        | Comments                                                                                                        |
|--------------|------------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------------------------------------------|------------------------------|------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Procaine     | Novocain (Winthrop Stearns); \$0.52/ml         | Para-aminobenzoic acid ester of diethylaminoethanol            | 0.5%<br>1%<br><b>2%</b>                                                                      | 1                            | Aqueous solutions are heat resistant<br>Decomposed by bacteria                                                   | Hydrolyzed by liver and plasma esterase<br>C = 36 mg/kg                                                         |
| Lidocaine    | Xylocaine (Astra Pharmaceuticals); \$0.0001/ml | Para-amino-2 chlorobenzoic acid ester of B-diethylaminoethanol | 1%<br><b>2%</b><br>2% PF<br>4% PF <sup>b</sup><br>10% PF <sup>b</sup><br>20% PF <sup>b</sup> | 2:1                          | Aqueous solutions are thermostable<br>Multiple autoclaving possible<br>Resistant to acid and alkaline hydrolysis | Absence of vasodilator effects makes addition of a vasoconstrictor unnecessary<br>C = 11–22 mg/kg IV            |
| Mepivacaine  | Carbocaine (Pharmacia-Upjohn); \$0.01/ml       | 1-methyl-2', 6'-pipecoloxylidide monohydrochloride             | 1% PF<br>1.5% PF<br>2% PF<br>1%<br><b>2%</b>                                                 | 2.5:1                        | Crystals and solutions should not be autoclaved                                                                  | Slow onset of anesthesia (5–10 min)<br>2-hr duration for eye instillation<br>C = 25–29 mg/kg IV                 |
| Bupivacaine  | Marcaine (Breon Laboratories); \$0.16/ml       | 1-butyl-2', 6'-pipecoloxylidide-HCl                            | <b>0.25%</b><br>0.5%                                                                         | 8:1                          | Stable                                                                                                           | Intermediate onset, lasting 4–6 hr<br>C = 3.5–5 mg/kg IV                                                        |
| Ropivacaine  | Naropin (Astra); \$0.30/ml                     | S-(—)-1-propyl-2', 6'-pipecoloxylidide-HCl monohydrate         | <b>0.2%</b><br>0.5%<br>0.75%<br>1%                                                           | 8:1                          | Stable<br>Hydrochloride salt of pure bupivacaine S(-) enantiomer                                                 | Intermediate onset, lasting 4–6 hr<br>Duration of anesthesia is inversely related to dose<br>C = 4.5–5 mg/kg IV |

<sup>a</sup>The most common preparations are in bold type.<sup>b</sup>Approved for use in humans.

C = convulsant dose in dogs (mg/kg); PF = preservative free.

Table 2. Local Anesthetic Delivery Systems<sup>a</sup>

| Product             | Manufacturer                            | Active Ingredient(s)                                    | Onset                  | Availability                                                                                                   | Uses                                                                    | Pros and Cons                                                                         |
|---------------------|-----------------------------------------|---------------------------------------------------------|------------------------|----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| EMLA Cream          | Astra Pharmaceuticals<br>Wilmington, DE | 2.5% lidocaine<br>2.5% prilocaine<br>(eutectic mixture) | 30–60 min<br>(minimum) | 5- and 30-g tubes<br>1-g disks                                                                                 | IV placement<br>Venipuncture<br>Short dermal<br>procedures <sup>b</sup> | Methemoglobin<br>formation<br>Occlusive dressing<br>Avg. 3-mm depth<br>Time to effect |
| ELA-Max<br>Cream    | Ferndale Laboratories<br>Ferndale, MI   | 4% lidocaine<br>(liposome<br>encapsulated)              | <20 min                | 5- and 30-g tubes                                                                                              | IV placement<br>Venipuncture<br>Short dermal<br>procedures              | Rapid onset<br>No dressing                                                            |
| Numby Stuff         | Iomed Inc.<br>Salt Lake City, UT        | 2% lidocaine<br>1:100000<br>epinephrine                 | 10 min                 | 1- and 2.5-ml<br>patches                                                                                       | IV placement<br>Venipuncture<br>Short dermal<br>procedures              | ~10-mm depth                                                                          |
| Lidoderm<br>Patch   | Endo Laboratories<br>Chadds Ford, PA    | 5% lidocaine                                            | Variable               | 700-mg, 10 × 14-cm<br>patch                                                                                    | Chronic pain<br>(neuropathic)                                           | 12 hr on, 12 hr off                                                                   |
| Pain Buster<br>ON/Q | I-flow Corp.<br>Lake Forest, CA         | Drug dependent                                          | Drug dependent         | Soaker catheter:<br>6.5–12.5-cm<br>infusion<br>Fill volumes:<br>65–335 ml<br>Flow rates:<br>0.5, 2, 4, 5 ml/hr | Postoperative<br>pain                                                   | Continuous delivery<br>Ambulatory<br>Fixed rate<br>± Prolonged drainage               |

<sup>a</sup>Contact specific manufacturers for a complete list of available products.<sup>b</sup>Procedures include minor wound repair, biopsy, and aspiration.

increase in the rate of infection.<sup>22-24</sup> Currently, several delivery systems are available for local analgesic therapy, including ambulatory electronic delivery, patient-controlled infusion, implantable local infusion, and ambulatory elastomeric delivery.<sup>21-25</sup> Each of these systems consists of slightly varying components that allow controlled, precise delivery of a drug to the region of interest. Current postoperative applications in human medicine include a wide variety of gynecologic, transplant, orthopedic, and gastrointestinal procedures.<sup>21-25</sup> Implantable systems are often used for treating chronic pain associated with neoplasia or neuropathic disease.<sup>25</sup>

Topically, the most commonly used local anesthetic in veterinary medicine is proparacaine for ocular anesthesia. In more recent years, percutaneous agents, such as EMLA cream or patches (2.5% lidocaine, 2.5% prilocaine; Astra Pharmaceuticals Ltd, Wilmington, DE), ELA-Max cream (4% liposome encapsulated lidocaine; Ferndale Laboratories Inc, Ferndale, MI), Lidoderm patches (4% lidocaine; Endo Laboratories, Chadds Ford, PA), and Numby Stuff patches (2% lidocaine, 1:100000 epinephrine; Iomed Inc, Salt Lake City, UT) have become available (Table 2). EMLA creams and patches are eutectic mixtures of lidocaine and prilocaine that allow greater tissue solubility and uptake.<sup>26,27</sup> This product is designed to penetrate the stratum corneum and provide superficial analgesia. It is commonly used to facilitate small wound repair, venipuncture, or catheter placement (IV, epidural) in small and exotic animals, particularly if systemic drugs are contraindicated.

It is recommended to apply the cream formulation under an occlusive dressing for at least 30 to 60 minutes before the desired procedure.<sup>27-29</sup> Depth of cutaneous analgesia is believed to be time dependent (1 to 4 hours), ranging from 1 to 6 mm.<sup>27</sup> Mixed clinical success has been reported in humans.<sup>26,27,29,30</sup>

ELA-Max cream consists of 4% lidocaine, which is liposome encapsulated to facilitate faster percutaneous absorption. Liposome encapsulation also allows the active ingredient to remain in the epidermis after application and minimizes rapid drug metabolism.<sup>29</sup> In addition, this preparation lacks the active ingredient prilocaine, which has been associated with methemoglobinemia in infants.<sup>28,29</sup> Because cats are more susceptible to methemoglobin formation, ELA-Max has been suggested as an attractive alternative to EMLA cream in this species.<sup>28</sup> No occlusive dressing is required with this preparation, and only 20 to 30 minutes are required for effect.<sup>28,29</sup>

Lidoderm patches, containing 5% lidocaine, are used primarily in human medicine for treating chronic neuropathic pain associated with postherpetic neuralgia.<sup>30</sup> Other reported uses include postthoracotomy and post-mastectomy analgesia in humans.<sup>30</sup> The patches are used in a 12 hours on, 12 hours off schedule to minimize systemic absorption. Single patches are 10 × 14 cm, with 700 mg of lidocaine per patch. Reported side effects include mild skin irritation. Use of this product in veterinary medicine has not been reported.

Numby Stuff is an iontophoretic system commonly

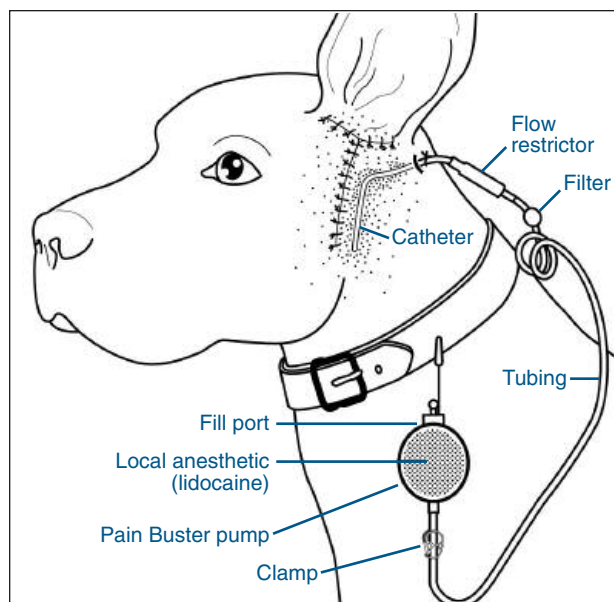


Figure 2A—Total ear canal ablation

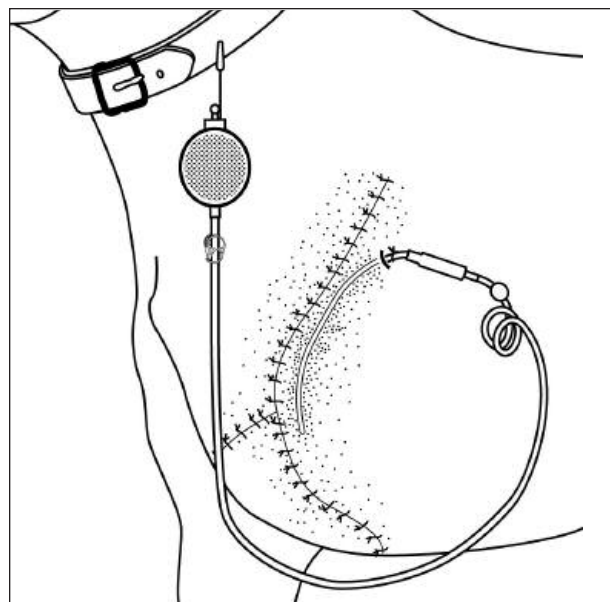


Figure 2B—Forelimb amputation

Figure 2—Applications of the Pain Buster local anesthetic infusion system.

used in human medicine to facilitate short percutaneous procedures. During iontophoretic drug administration, a small electrical current (4 mA) is administered through a battery generator and two small electrodes to facilitate rapid percutaneous drug uptake.<sup>26,31</sup> Following 10 minutes of delivery, anesthetic depths up to 10 mm have been documented.<sup>31</sup> This technique allows more rapid onset of action with greater depth of local anesthesia/analgesia. Each application device delivers 1 ml of 2% lidocaine and 1:100,000 epinephrine to the region. The effect of delivery is felt immediately, with associated transient blanching and tingling of the skin. Use of this system is contraindicated in patients with pacemakers. Although veterinary application of this product has not been published, potential uses include catheter placement and epidural placement.

The Wand (Milestone Scientific, Livingston, NJ) is a popular means of applying local nerve blockade in human dentistry and minor perianal procedures.<sup>32</sup> This pen-like delivery device contains a needle/syringe apparatus under computer control. This allows controlled delivery pressure and volume ahead of the needle tip to minimize the pain associated with injection. Various administration volumes are available. Use of this product in veterinary medicine has not yet been described.

The Pain Buster/ON-Q (I-flow Corp, Lake Forest, CA) local anesthetic delivery system includes a radioopaque, fenestrated catheter that is placed in the surgical wound under direct visualization just before wound closure (Figure 2). This is attached to an extension set containing a filter and flow restrictor. The attached drug reservoir is a disposable elastomeric bulb designed to deliver a known volume of drug each hour. Variable infusion bulbs and flow rates are available. A preliminary pilot study, including 17 dogs undergoing total ear canal ablation, amputation, and median and lateral thoracotomies, was conducted. The first two patients received ropivacaine infusions, whereas all subsequent patients received lidocaine. Many of these patients recovered quickly and comfortably, requiring little to no supplemental analgesics. All infusion systems were well tolerated by the patients, and little (if any) breakthrough pain was reported. Mild signs of lidocaine toxicity were noted in one patient that developed nystagmus several hours postoperatively but responded quickly to removal of the Pain Buster catheter. It was later determined that incomplete drug reservoir filling may have contributed to an inappropriate drug delivery rate. Reported disadvantages of elastomeric infusion systems in humans include prolonged wound drainage, inability to alter delivery rate, and difficulty in identifying and monitoring increases or delays in the rate of infusion.<sup>21,23</sup> Ongoing work evalu-

ating these systems as a sole means of providing postoperative analgesia to dogs is currently being conducted. However, our initial experience supports their use in selected clinical patients.

## SUMMARY

As local anesthetic usage increases among small animal practitioners, the methods for applying such drugs will increase. Alternative local anesthetic delivery systems, such as Pain Buster/ON-Q, could become an integral component of analgesic therapy in veterinary practice. Use of such systems should improve the quality of analgesia while minimizing the systemic effects and overall need for supplemental systemic therapy.

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### ARTICLE #3 CE TEST

The article you have read qualifies for 1.5 contact hours of Continuing Education Credit from the Auburn University College of Veterinary Medicine. *Choose the best answer* to each of the following questions; then mark your answers on the postage-paid envelope inserted in *Compendium*.

1. Which of the following is not a potential sequela to pain?
  - a. improved wound healing
  - b. decreased bowel motility
  - c. cardiorespiratory compromise
  - d. immunosuppression
  - e. elevations in blood glucose
2. Secondary hyperalgesia
  - a. describes pain that is localized to the site of injury.
  - b. describes pain that is felt outside of the injured area.
  - c. can be prevented by using local anesthetics.
  - d. results in pain that is easier to manage.
  - e. both b and c
3. Potential systemic effects of traditional analgesics (opioids) may include
  - a. sedation.
  - b. emesis.
  - c. respiratory depression.
  - d. ileus.
  - e. all of the above
4. Local anesthetics of the amide group
  - a. include procaine, tetracaine, and lidocaine.
  - b. require glucuronic acid conjugation for breakdown.
  - c. are hydrolyzed in plasma.
  - d. are more commonly associated with allergic response.
  - e. are not eliminated by the kidney.
5. Side effects of local anesthetic agents
  - a. can include hypotension, arrhythmia, methemoglobinemia, and seizure.
  - b. are common.
  - c. are less likely with IV delivery.
  - d. are least likely with benzocaine and prilocaine.
  - e. are not reported.
6. Which of the following is false?
  - a. Some local anesthetics have antimicrobial effects.
  - b. The addition of bicarbonate to local anesthetics is associated with a more rapid onset and shorter duration of analgesia.
  - c. The addition of epinephrine to local anesthetics hastens the rate of vascular absorption and lessens the duration of action.
  - d. More lipophilic local anesthetics are more potent.
  - e. Local anesthetics act by blocking sodium channels.

7. Reported disadvantages of elastomeric local drug delivery include all of the following except
  - a. prolonged wound drainage.
  - b. fixed delivery rate.
  - c. difficulty in monitoring rate of infusion.
  - d. increased rate of infection.
  - e. none of the above
8. EMLA cream
  - a. contains a eutectic mixture of lidocaine and prilocaine.
  - b. consists of liposome-encapsulated lidocaine.
  - c. uses iontophoresis to promote drug delivery.
  - d. does not require application under an occlusive dressing.
  - e. requires 10 minutes to become effective.
9. ELA-Max cream
  - a. requires application beneath an occlusive dressing.
  - b. is liposome-encapsulated to prolong its duration of action.
  - c. contains prilocaine, which has been associated with methemoglobinemia.
  - d. is liposome-encapsulated to facilitate more rapid absorption.
  - e. all of the above
10. Numby Stuff
  - a. is an iontophoretic drug delivery system.
  - b. contains a combination of lidocaine and epinephrine.
  - c. can penetrate to a depth of up to 10 mm.
  - d. uses an electric current to promote drug delivery.
  - e. all of the above