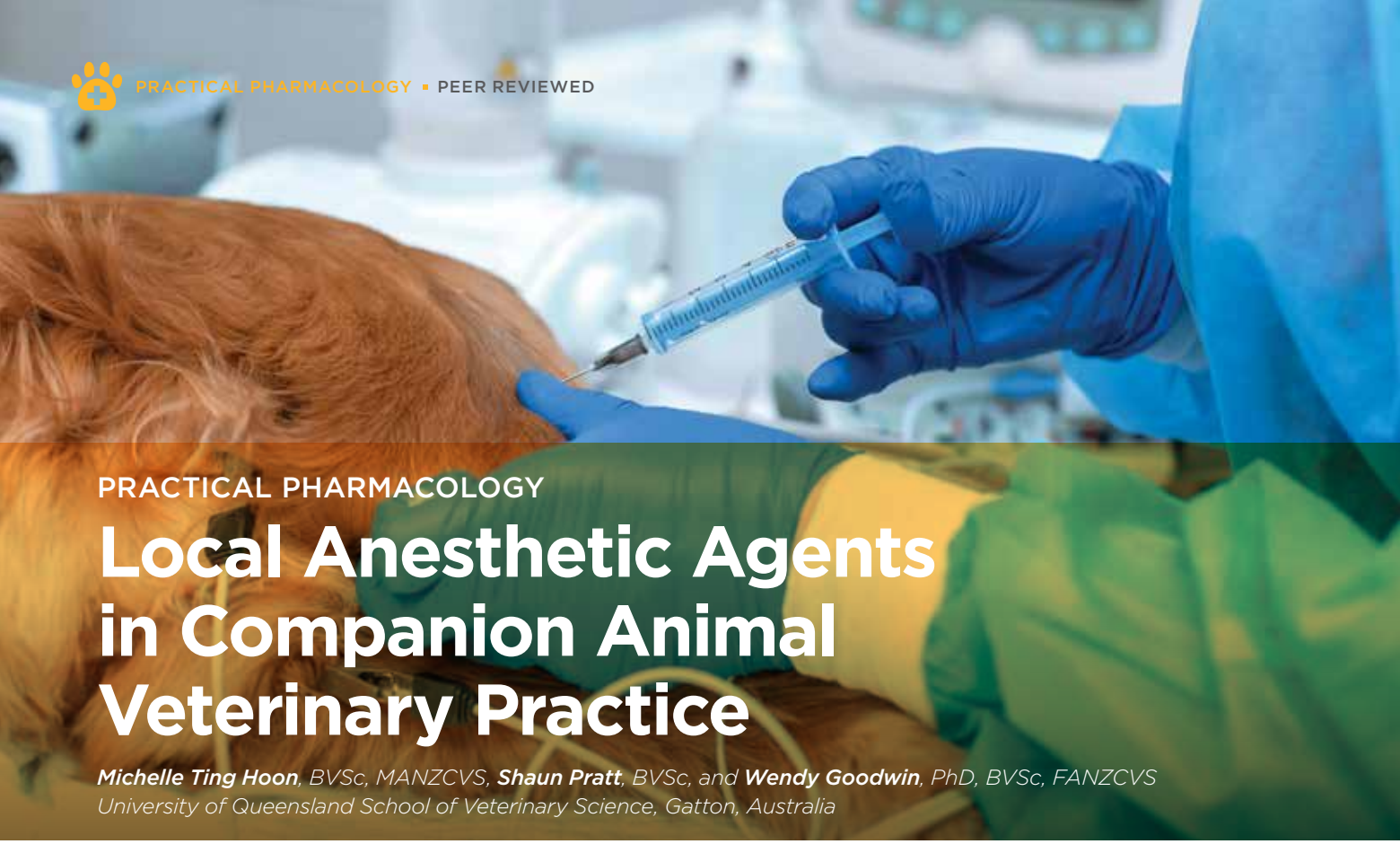

PRACTICAL PHARMACOLOGY

Local Anesthetic Agents in Companion Animal Veterinary Practice

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Local anesthetic (LA) agents work by reversibly inhibiting nerve impulse conduction and produce locoregional anesthesia through local tissue desensitization. LA agents are inexpensive, are widely available, improve anesthetic quality, contribute to multimodal analgesia, and have opioid-sparing benefits when used effectively. It is therefore important for veterinary professionals across all disciplines to understand how LA agents work and the risks for toxicity.

Commonly used LA agents in small animal veterinary practice include lidocaine, prilocaine, mepivacaine, ropivacaine, and bupivacaine. They are available in injectable and topical formulations and may be combined with vasoactive additives such as epinephrine. This article provides general indications and risks associated with LA agent use. Technical information on peripheral nerve blocks and a detailed description of advanced routes of LA agent administration are published elsewhere.[1,2]

MECHANISM OF ACTION AND PHARMACOLOGIC PROPERTIES

The time to onset, duration of action, and risk for toxicity vary between formulations and largely depend on the pK_a (the negative log of the acid dissociation constant [K_a]), protein binding, and lipid solubility of the LA agent.[2] These physiochemical properties are shown in **TABLE 1** for common LA agents. In general, LA agents reversibly bind to voltage-gated sodium channels on the cell membrane of nerve axons to prevent the influx of sodium ions. Consequently, the initiation and propagation of action potentials are inhibited, resulting in a reversible interruption to nociceptive conduction and thus blocking transmission of pain impulses (**FIGURE 1**).

Abstract

Local anesthetic (LA) agents are an important part of multimodal analgesic protocols in veterinary practice. This article provides an overview of commonly used LA agents and their indications and recommended doses, as well as steps to prevent local anesthetic systemic toxicity.

Take-Home Points

- Local anesthetic (LA) agents work by reversibly inhibiting nerve impulse conduction.
- LA agents are inexpensive and widely available, improve anesthetic quality, contribute to multimodal analgesia, and have opioid-sparing benefits.
- Several steps can be taken to avoid local anesthetic systemic toxicity, including adhering to maximum dose recommendations, being aware that drug absorption varies between injection sites, and avoiding mixing LA agents.
- Lidocaine can be used intravenously in dogs to provide systemic analgesia, ventricular antiarrhythmia treatment, and multiorgan dysfunction attenuation.

Susceptibility to LA agents varies between types of nerves. Briefly, narrow-diameter myelinated sensory fibers (classified as Aδ) and nerves of the autonomic nervous system are more susceptible to LA agents than larger-diameter pressure fibers (Aβ), motor fibers (Aα), and unmyelinated chronic pain fibers. This explains why a differential block between sensory and motor nerve groups can be appreciated following the injection of many LA agents.

The time to onset of an LA agent depends on the agent's ability to penetrate the nerve cell, as LA agents bind to the internal aspect of the transmembrane sodium channel (**FIGURE 1**). The duration of action is determined by affinity for the sodium channel and overall lipid solubility. The toxicity of LA agents is determined by accumulation within cardiomyocytes and cells of the central nervous system (**TABLE 1**). Detailed descriptions of the physiochemical properties of LA agents and how these affect their pharmacokinetic properties are published elsewhere.[1,4]

ROUTES OF ADMINISTRATION

Locoregional anesthesia using LA agents can be achieved by topical application, local infiltration into tissues (e.g., subcutaneous infiltration, incisional line block, wound diffusion catheters, splash blocks) and cavities (intrasynovial and intra-articular), intravenous local or regional anesthesia (Bier block), or targeted peripheral perineural (nerve block) and central neuraxial (epidural and subarachnoid) injections. Additionally, some LA agents, such as lidocaine, can be administered systemically via intravenous route for acute perioperative pain management and to aid in the treatment of certain cardiac arrhythmias in dogs.

LOCAL ANESTHETIC SYSTEMIC TOXICITY

Central nervous system and cardiovascular disturbances are the most common adverse effects associated with local anesthetic systemic toxicity (LAST) and usually result from inadvertent IV injection, rapid systemic absorption, or absolute overdosing. Allergic reactions may also occur. Central nervous system signs usually appear first and include sedation, muscle tremors, and/or seizures. The cardiovascular effects usually follow and result from direct blockade of myocardial sodium channels. This causes bradyarrhythmia and reduced myocardial contractility; however, immediate sympatholysis and vasodilation can be seen following

TABLE 1 Physiochemical Properties of Commonly Used Local Anesthetic Agents[a]

LOCAL ANESTHETIC	pK_a	ONSET TIME (MIN)	PROTEIN BINDING (%)	DURATION (MIN)	LIPID SOLUBILITY	TOXICITY RISK
Lidocaine	7.9	5	70	60–120	366	Low
Prilocaine	7.7	5	55	60–90	129	Low
Mepivacaine	7.6	10	75	90–120	130	Low
Ropivacaine	8.1	20	95	360–480	775	Medium
Bupivacaine	8.1	20	95	360–480	3420	High

[a]The duration of action for the local anesthetic (LA) agents listed above should serve as a guide only. If perioperative analgesia relies on locoregional anesthesia provided by an LA agent, routine patient pain scoring is recommended.[3] pK_a = negative log of the acid dissociation constant (K_a)

neuraxial anesthesia. Bupivacaine binds to the sodium channel with greater affinity than lidocaine or ropivacaine and dissociates more slowly, ultimately resulting in prolonged conduction and reentry-induced arrhythmias.[1]

In cases of tremors or seizures, intravenous volume expansion, supportive care, and standard use of antiepileptic drugs are indicated. Intubation, ventilation, and oxygenation may be required. In cases of cardiopulmonary arrest following suspected LAST, intravenous lipid emulsion (ILE) has been shown to improve survival when used in combination with standard cardiopulmonary resuscitation.[5] The rapid rise in lipemia is thought to reduce active LA agent in the blood and tissues. Increases in free fatty acids available to the myocardium for oxidative phosphorylation may also contribute. A loading dose of 1.5 to 2 mL/kg followed by an infusion of 0.25 mL/kg/min of commercially available 20% ILE has been used successfully in dogs and cats to treat a range of lipophilic toxicoses, including LAST. Constant rate infusions (CRIs) have been maintained for 30 minutes in cats and for up to 90 minutes in dogs.[6,7] Considerations for ILE use include pancreatitis, marked lipemia, lipid embolism, and allergic reactions.

A process known as ion trapping can occur in pregnant animals, particularly during fetal distress. A reduction in fetal pH increases the ionization of the LA agent in the fetal circulation, leading to its accumulation. All LA agents undergo this phenomenon to varying degrees. Generally, the use of less toxic LA agents is recommended in pregnant animals; administration of IV doses of lidocaine is not recommended.

Prevention of LAST is paramount, and several steps can be taken to reduce its risk:

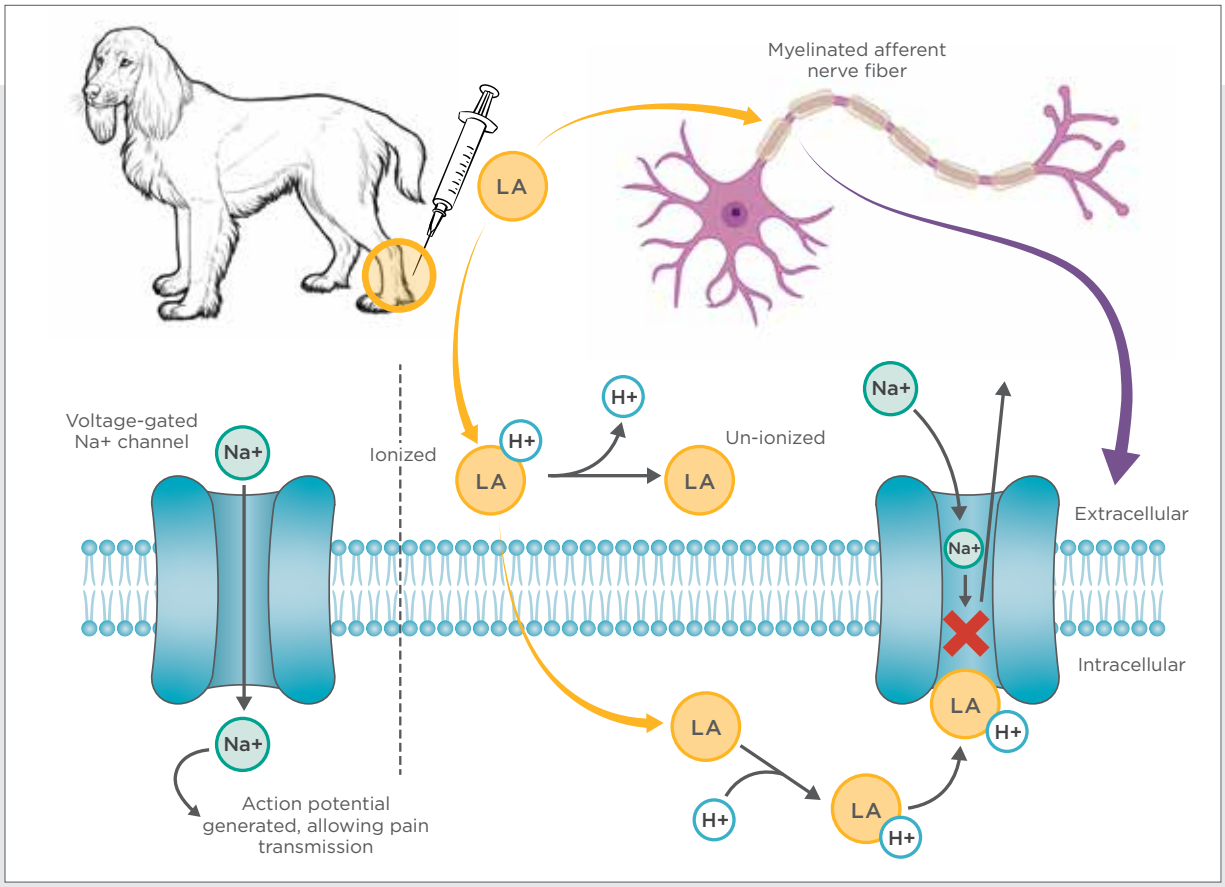

FIGURE 1. Mode of action of local anesthetic (LA) agents. Diffusion through the phospholipid bilayer of neurons depends on the un-ionized concentration of the LA agent, which is determined by the pK_a. In general, LA agents with a pK_a similar to physiological pH (7.4) rapidly diffuse into the cell and have faster onset times. For example, lidocaine (pK_a 7.9) has a faster onset of action than bupivacaine (pK_a 8.1) because at a pH of 7.4 more of the drug is present in the un-ionized form.
H+ = hydrogen ion; NA+ = sodium ion; pK_a = negative log of the acid dissociation constant (K_a).

Dog: HeatherWolf/shutterstock.com; Syringe: Net Vector/shutterstock.com

- Aspirate prior to injection of the LA agent to avoid inadvertent intravascular injection.
- Adhere to maximum dose recommendations for the specific agent and consider the physiologic status of the individual patient. For example, neonates have reduced liver metabolism and lower plasma protein and thus are at an increased risk of LAST.
- Consider concurrent use of vasoconstrictors (e.g., epinephrine) to reduce the systemic absorption of the LA agent.
- Take care when using multiple regional blocks in a single patient and be aware that drug absorption varies between injection sites. For example, high plasma concentrations of LA agents occur with intercostal, epidural, and brachial plexus blocks.
- Avoid mixing LA agents, as the toxicity risk of combining multiple agents is not known but should be assumed to be additive (**BOX 1**).
- In humans, international consensus guidelines on the safety of IV lidocaine infusions exist and recommend careful patient monitoring, slow administration of the loading dose, not starting IV lidocaine within 4 hours of regional nerve block (or vice versa), and continuing the infusion for a maximum of 24 hours.[10]

BOX 1 Should Local Anesthetic (LA) Agents Be Mixed?

It has been suggested that mixing bupivacaine and lidocaine provides the best of both worlds—the fast onset of lidocaine with the long duration of action of bupivacaine. However, when pharmacokinetics is considered, this practice cannot be recommended. Mixing LA agents alters the pH and reduces the concentration gradient and thus affects onset time, penetration into nerves, and duration of action. Peer-reviewed reports also discourage mixing LA agents, and expert consensus is that "the best of both worlds" is not achieved.[8,9]

COMMONLY USED AGENTS

Lidocaine Hydrochloride

Background: Commonly available as a 1% (10 mg/mL) or 2% (20 mg/mL) hydrochloride solution formulated alone or in combination with epinephrine. Generally, lidocaine has a rapid onset and short duration of action. The addition of local vasoconstrictor agents (e.g., epinephrine, α_2-receptor agonists) can prolong lidocaine's duration of action and inhibit the intrinsic local vasodilation.

Indications: Topical application onto cutaneous skin, local infiltration into tissues or cavities, Bier block, peripheral perineural injection, and central neuraxial injection. Injectable formulations can be used intravenously for their antiarrhythmic and analgesic properties in dogs.

Recommended doses and safety: Subcutaneous and peripheral perineural injections of up to 6 to 8 mg/kg in dogs and 3 to 5 mg/kg in cats are generally recommended. Topical spray products are registered for use in cats to achieve laryngeal desensitization prior to intubation; however, the authors recommend caution in cats weighing less than 2 kg, given the relatively large cumulative dose that can be administered with sprays. Neuraxial epidural injections of up to 4 mg/kg in dogs and cats are generally recommended and are often combined with morphine (0.1 to 0.2 mg/kg) or buprenorphine (0.01 to 0.02 mg/kg). Generally, the maximum recommended volume in dogs is 6 to 7 mL.

Rapid IV injections of 22 mg/kg in dogs and 11 mg/kg in cats have produced seizures.[1] Often, loading doses of 1 to 2 mg/kg IV administered slowly followed by CRI doses of 10 to 50 µg/kg/min are used in dogs. Due to the increased risk of toxicity in cats, caution should be used when considering systemic use of lidocaine in cats. Administration via syringe pump to allow for more accurate dosing is generally recommended. If a syringe pump is not available, lidocaine can be added to a bag of 0.9% saline for CRI (**BOX 2**). Lidocaine is light sensitive; therefore, the fluid bag or syringe should be kept covered if long-term use is expected.

Take care when using multiple regional blocks in a single patient and be aware that drug absorption varies between injection sites.

BOX 2. Steps to Set Up a Lidocaine CRI Using a Fluid Pump

Example: Desired infusion rate: 10 µg/kg/min in a 20-kg dog.

1. Remove 50 mL of 0.9% saline from a 1 L fluid bag.
2. Add 1000 mg (50 mL) of 2% lidocaine to the bag to achieve a concentration of 1 mg/mL.
3. Set the fluid pump to run at 12 mL/hr.

CRI = constant rate infusion

Multiple studies have shown the benefits of using lidocaine–prilocaine topical cream combinations for reducing pain associated with venipuncture in cats and dogs when approximately 1 cm^2 of the formulation is applied to the skin overlying the vessel.[11,12] However, care needs to be taken to prevent accidental ingestion. The hydrolysis of prilocaine releases ortho-toluidine, which oxidizes hemoglobin and results in clinically significant methemoglobinemia in children. A study by Gibbon et al. reported no methemoglobinemia in feline patients following the use of lidocaine–prilocaine cream[13]; however, given that transmucosal and transdermal absorption are dissimilar, the application of an occlusive bandage is recommended to decrease the risk of accidental ingestion. Lidocaine transdermal patches are available, but evidence supporting their clinical use in dogs is limited.[14,15]

Special notes: Lidocaine is classified as a class 1 antiarrhythmogenic drug and can be used to aid in the treatment of ventricular premature complexes and ventricular tachycardia. As previously mentioned, lidocaine may provide effective perioperative analgesia in dogs, although the mechanism is poorly understood.[16] Additionally, lidocaine may be combined with opioids (e.g., morphine, fentanyl, methadone) and/or dissociative anesthetic agents (e.g., ketamine) for advanced perioperative pain management.

Experimentally in other species (pigs and humans), lidocaine reduces the concentration of systemic inflammatory mediators and reduces the risk for multiorgan dysfunction (MODS) following hypoxic reperfusion injury.[17,18] Lidocaine's potential benefit for MODS attenuation during gastrointestinal surgery in dogs is inconclusive, yet promising. The anesthetic-sparing effects (minimum alveolar concentration [MAC] reduction) of lidocaine may only be appreciable at higher doses (5 to 6 mg/kg/h) and often provide an insubstantial effect (<20% MAC reduction) compared with opioids and dissociative anesthetic agents.[19,20] Higher doses of lidocaine (12 mg/kg/h) that have increased MAC reduction generally result in vomiting and ataxia in recovery.

Lidocaine has been combined with α_2 receptor agonists such as dexmedetomidine to increase the duration (approximately 300 minutes) of peripheral nerve blockade in dogs.[21] This may be helpful when longer-acting LA agents such as bupivacaine or ropivacaine are unavailable or are contraindicated. Care should be taken when using these formulations (in addition to commercially available lidocaine–epinephrine formulations) in regions where collateral circulation is poor, such as the tail.

Mepivacaine Hydrochloride

Background: Commonly available as a 2% (20 mg/mL) hydrochloride solution. Mepivacaine has a fast onset and intermediate duration of action.

Indications: Topical application, local infiltration into tissues or cavities, and peripheral perineural injection.

Recommended doses and safety: Peripheral perineural injections of up to 6 mg/kg in dogs and 3 mg/kg in cats are generally recommended. The perineural dose reported to cause seizures is 29 mg/kg.[1] Mepivacaine should not be administered intravenously. Intra-articular doses of 1 to 2 mg/kg are commonly used clinically.

Special notes: Mepivacaine is considered minimally chondrotoxic and results in less tissue irritation and vasodilation than lidocaine or bupivacaine. It is commonly used for intra-articular and intrasynovial injections, particularly in horses.

Ropivacaine Hydrochloride

Background: Commonly available as a 0.2% (2 mg/mL), 0.75% (7.5 mg/mL), or 1% (10 mg/mL) hydrochloride solution. Ropivacaine has a slow onset and long duration of action.

Indications: Local infiltration into tissues or cavities, peripheral perineural injection, and central neuraxial injection.

Recommended doses and safety: Peripheral perineural injections of up to 3 mg/kg in dogs and 2 mg/kg in cats are generally recommended. Ropivacaine should not be administered intravenously. Neuraxial epidural injections of up to 1 mg/kg are generally recommended and are often combined with morphine (0.1 to 0.2 mg/kg) or buprenorphine (0.01 to 0.02 mg/kg).

Special notes: Ropivacaine is considered the least chondrotoxic LA agent and is commonly used for intra-articular and intrasynovial injections. Ropivacaine has a slightly lower lipophilicity than bupivacaine, meaning the motor blockade produced by ropivacaine may be less profound and of shorter duration.[22] For this reason, ropivacaine is the LA agent of choice at the authors' institution for the provision of neuraxial analgesia and peripheral nerve desensitization.

Bupivacaine Hydrochloride

Background: An equimolar racemic mixture of R- and S-enantiomers commonly available as a 0.25% (2.5 mg/mL), 0.5% (5 mg/mL), or 0.75% (7.5 mg/mL) hydrochloride solution. Bupivacaine has a slow onset and long duration of action.

Indications: Local infiltration into tissues or cavities, peripheral perineural injection, and central neuraxial injection.

Recommended doses and safety: Perineural injections of up to 2 mg/kg are generally recommended in dogs and cats. Bupivacaine should not be administered intravenously due to its profound cardiotoxicity. Compared with lidocaine, bupivacaine causes significant myocardial depression and arrhythmogenicity. Epidural injections of up to 1 mg/kg are generally recommended and are often combined with morphine (0.1 to 0.2 mg/kg) or buprenorphine (0.01 to 0.02 mg/kg).

Special notes: Levobupivacaine contains only the S-enantiomer of the bupivacaine molecule. It is considered slightly less cardiotoxic; however, IV administration is still not recommended.

Liposomal encapsulation delays systemic absorption and prolongs activity at the site of injection. Encapsulation prevents diffusion through tissue planes until the active ingredient is released.

Bupivacaine Liposome Injectable Suspension (BLIS)

Background: BLIS is available as a 13.3 mg/mL extended-release formulation (Nocita; Elanco, elanco.us).

Indications: Registered for local infiltration into the tissue planes following cruciate ligament surgery in dogs and prior to onychectomy in cats, administered as a 4-point block.

Recommended doses and safety: Local infiltration of 5.3 mg/kg (0.4 mL/kg) for the provision up to 72 hours of nerve desensitization (analgesia). Sterile saline can be used to increase the volume to cover the entire surgical area in dogs. BLIS should not be administered intravenously or as a neuraxial injection.

Special notes: Reported adverse reactions include discharge from the incision, incisional inflammation, proteinuria and vomiting in dogs, and pyrexia in cats. Liposomal encapsulation delays systemic absorption and prolongs activity at the site of injection. Encapsulation prevents diffusion through tissue planes until the active ingredient is released. Therefore, effective analgesia outside the tissue plane of injection is delayed. A detailed review of BLIS has been published elsewhere.[23]

SUMMARY

LA agents are affordable and readily available, and they play an important part of a multimodal analgesic protocol. Various formulations of LA agents are available. Toxicity, while generally uncommon, can occur, and several steps can be implemented to improve

patient safety. Additional benefits to locoregional anesthesia provided by LA agents include opioid-sparing, balanced anesthesia and improved patient outcomes. Systemic analgesia, ventricular antiarrythmia treatment, and MODS attenuation are additional benefits of IV administration of lidocaine in dogs. TVP

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