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LOCAL ANESTHETICS, PHARMACOLOGY AND SPECIAL PREPARATION

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ABSTRACT

Local anesthetics are used for the presentation of various regional anesthesia practices for intraoperative anesthesia and analgesia, along with the treatment of acute and chronic pain. Older medications like lidocaine and bupivacaine as well as newer ones such as mepivacaine and ropivacaine are being used successfully for decades. Routes of administration contain neuraxial, perineural, intravenous, various infiltrative approaches, topical, and transdermal. There is new innovation with the use of older local anesthetics in novel manners, in addition to the development and use of new formulations. This article seeks to summarize the history, physical properties, mechanism of action and pharmacokinetics, toxicity, finally, some special preparation.

KEYWORDS: Lidocaine patch, Liposomal bupivacaine, Exparel, Local anaesthetics, Nocita, Pharmacology.

INTRODUCTION

An anaesthetic is a drug that can act on the nervous system and inhibit it and is thus a drug that produces anaesthesia.[1,2] Local anaesthetics act on nerve endings and nerve trunks and can reversibly block the conduction of nerve impulses. This results in a loss of local sensation without affecting consciousness, which is convenient for local surgery and treatment.[3–5] Local anaesthetics are commonly used in stomatology, ophthalmology, gynaecology and minor surgical operations to temporarily relieve pain.[6–9] Local anaesthetics bind to specie parts of the sodium ion (Na+) channel on the nerve membrane and affect the membrane potential by reducing the passage of sodium ions through the sodium ion channel, and thereby block the conduction of nerve impulses. Local anaesthetics can reduce the excitability of the membrane and have no effect on the resting potential.[10–14]

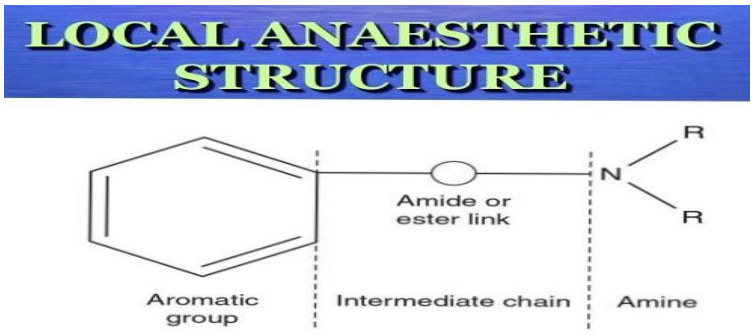

Fig. 1: General structure of local anaesthetics.

History

The first local anaesthetic that was used in clinical practice comprised active ingredients derived from coca leaves from South America. As early as the 16th century, Peruvians were known to chew coca leaves to relieve pain. In the 1860s Niemann extracted crystals of an alkaloid from coca leaves and named it as cocaine.[15–17] In 1868 Maiz was the first to suggest that cocaine might be a local anaesthetic, and in 1884 Koller (an Austrian ophthalmologist) was the first to use cocaine for clinical surgery, which led to the discovery of new anaesthesia techniques and the rapid development of local anaesthetic drugs.[18–21] However, in the process of use, cocaine was found to cause addiction and some other toxic effects, such as allergic reactivity, tissue stimulation and instability in aqueous solutions. Hence, the clinical application of cocaine was limited. As a result, structural studies and medications of cocaine have been carried out in the search for better local anaesthetics. From studies of the structure of cocaine, it

was gradually realized that the removal of the methyl carboxylate group in the structure of cocaine could eliminate addiction. The local anaesthetic effect of ethyl-4-aminobenzenecarboxylate (benzocaine) was first confirmed in 1890, and procaine was successfully developed in 1904. The discovery of procaine made people realize the important role of the 4-aminobenzoate structure in local anaesthetic drugs and started the study of the 4-aminobenzoate structure.[22–24] (tetracaine) and the development of local anaesthetic drugs with amide,[25,26] (lidocaine), aminoketone,[27] (dyclonine) and amino-ether,[28,29] (pramocaine) structures (Fig. 2).

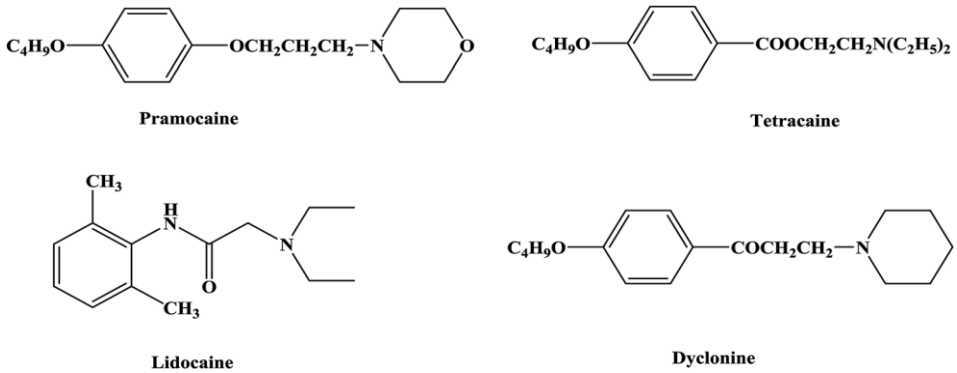

Fig. 2: Chemical structure of some local anaesthetics.

Physical Properties

Local anaesthetics are weak bases with a pKa (dissociation constant) of 7.5 to 8.5, and are divided into 2 categories based on their structure: aminoamides or amino-esters. The general structure of all agents consists of an aromatic group connected to a tertiary amine via an amide linkage (aminoamide) or an ester linkage (amino-ester). Four physicochemical properties determine the activity of local anaesthetic agents: molecular weight (MW), pKa, lipid solubility, and degree of protein binding. Ranging from 220 to 288 Da, the MW is inversely related to the ability of the local anaesthetic to diffuse through tissue. Just as changes in MW are caused by differing substitutions on the aromatic group and tertiary amine, changes in MW are generally also associated with changes in pKa and lipid solubility.[30] As weak bases, local anaesthetics equilibrate into ionized and nonionized molecules within the body in accordance with their pKa. By definition, the pKa is the pH at which the drug is at equilibrium with 50% in the ionized form and 50% in the nonionized form. The local anaesthetic binding site on the sodium channel is within the cell and the drug must diffuse into the target neuron cell body to have an effect. It is the nonionized form of the drug that can easily cross the cell membrane.[31] and, once inside the cell, a new equilibrium is established and the ionized (active) form of the drug can take effect.[32] In general, agents with a low pKa will have a rapid onset of action due to a lower degree of ionization at physiologic pH and agents with a high pKa will have a slower onset of action due to the greater degree of ionization at physiologic PH. The structure of the aromatic group is the main determinant of the agent's solubility. The degree of solubility is extremely important because it determines the potency.[32] and duration of action of the agent.[33] Agents with low lipid solubility have low potency and a shorter duration of action. Agents with high lipid solubility tend to be more potent and afford a longer duration of action. Lipid solubility also affects onset of action in that highly lipid soluble agents are more likely to be sequestered in myelin, slowing the arrival of the agent at the neuronal membrane and prolonging the onset of action. The degree of protein binding determines the free fraction of drug available to bind to the target receptors and cause an effect. In general, agents that are highly protein bound are associated with a longer duration of action.[34]

Mechanisms of Action and Pharmacokinetics

Local anaesthetics diffuse across the plasma membrane and reversibly inhibit voltage gated sodium channels. Typically, electrical neuronal excitation conducts a depolarizing stimulus down the axon, activating and permitting sodium ions to cross down their electrochemical gradient. Local anaesthetics interrupt the action potential and thus the influx of sodium ions, thereby decreasing the excitability of the nerves conducting pain responses.[35] Both motor and sensory blockade are obtained in this manner. Myelinated axons are easily blocked by local anaesthetics, followed by unmyelinated axons. The first documented medical use of a local anaesthetic occurred in 1884, when Dr. Carl Koller anesthetized the cornea with topical cocaine solution.

A local anaesthetic molecule is composed of three parts: a lipophilic aromatic ring, an ester or amide link, and a terminal amine.[36] A hydrocarbon chain is linked to the aromatic ring via either an ester or amide connection, which determines the mechanism of metabolism for that local anaesthetic. Amide local anaesthetics have been shown to be more chemically stable and have a lower risk of allergic reactions, in comparison to ester local anaesthetics. Ester amides are primarily metabolized by plasma cholinesterase, otherwise known as pseudocholinesterase.

Degradation is quite rapid. In comparison, amide local anaesthetics undergo hepatic degradation and have a longer half-life. Local anaesthetics are nature weak bases (with the exception of benzocaine) formulated in an acidic solution. A lower pKa yields a higher fraction of the neural drug that can cross the membrane, whereas the charged protonated form binds the target firmly. A more basic pKa is associated with a slower onset. The substitutions on the aromatic ring directly correlate with lipid solubility. Improved diffusion across the nerve is associated with increased potency. Higher hydrophobicity improves transport to target site, and thusly, higher potency. The duration of action is connected to the level of protein binding.

Local anaesthetics are not only sodium channel blockers. They have anti-inflammatory and possible antimetastatic properties.[37,38] It has also been shown to have a role in chronic pain conditions such as neuropathic pain and complex regional pain syndrome.[39,40] Research shows that they interact with other receptors as well. It has been demonstrated that the analgesic and anti-hyperalgesic properties of intravenous lidocaine infusions involve in addition to the sodium channel blockade, the inhibition of potassium and calcium channels, the glycinergic system, the NMDA and the Gaq-coupled protein receptors.[41,42]

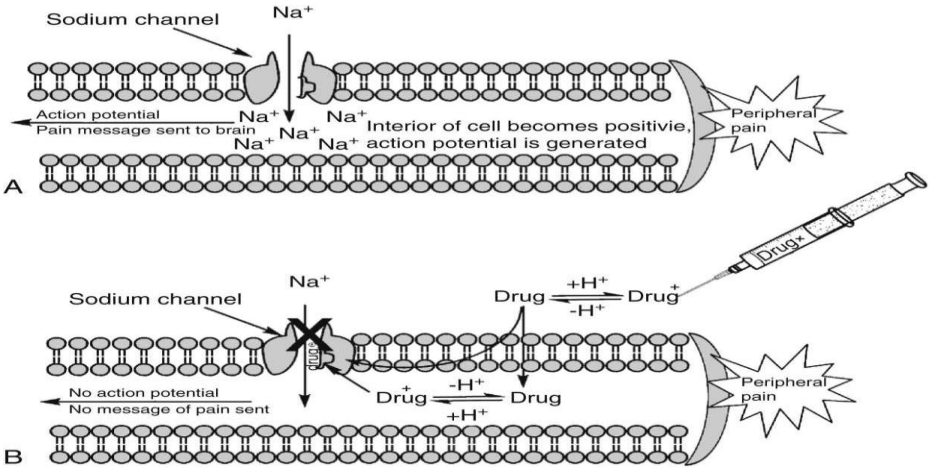

Fig. 3: Mechanism of action of Local anaesthetics.

Pregnancy and local anaesthetics

Increased sensitivity to local anaesthetics, demonstrated as faster onset and more profound block, may be present during pregnancy. Variations in protein binding of bupivacaine may result in amplified concentrations of active unbound drug in the pregnant patient, increasing its dormant for toxicity. Placental transfer is also more active for lipid soluble local anaesthetics. In any case, agents with a pka closer to physiologic pH have a higher placental transfer. As a result, the umbilical maternal vein ratio for mepivacaine (pka 7.6) is 0.8, while for bupivacaine (pka 8.1) is 0.3. In the presence of foetal acidosis, local anaesthetics cross the placenta and become ionized in higher proportion than at normal PH. The ionized portion can't cross back to the maternal circulation, originating what is called "ion trapping". Therefore, 2-chloroprocaine, with its very short maternal and foetal half-lives, is an ideal local anaesthetic in the presence of foetal acidosis.[43]

TOXICITY

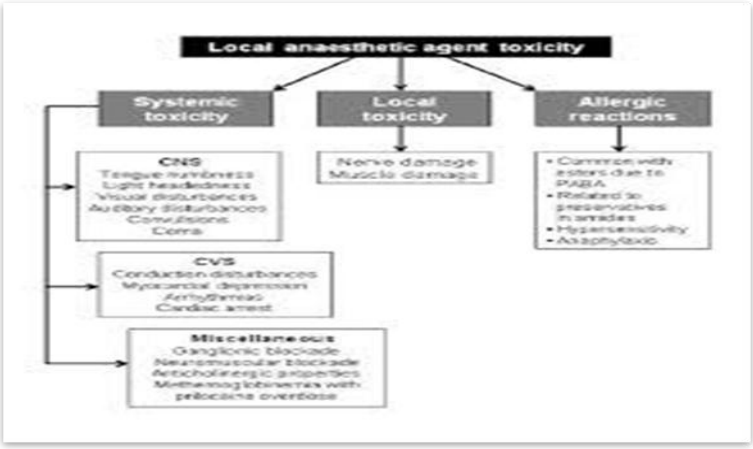

Fig. 4: Toxicity of local anaesthetics.

Systemic Toxicity

Administration of local anaesthetics can cause neurotoxicity and cardiotoxicity as plasma levels increase. Neurotoxicity results from the action of local anaesthetics blocking inhibitory pathways within the brain, which leads to unopposed excitatory activity with clinical signs, such as twitching and seizures.[44] As plasma levels continue to increase, cardiotoxic effects will occur due to blockade of sodium channels, resulting in a decrease in the rise of phase 0 of the cardiac action potential.[45] Associated changes on the electrocardiogram (ECG) may be observed, including prolonged PR and QRS intervals.

In general, systemic toxicity is more likely to occur with agents having high lipid solubility (i.e. bupivacaine, etidocaine, tetracaine). Additionally, the S-enantiomers are less toxic than the R-enantiomers, making levobupivacaine and ropivacaine safer than their dextrorotary counterparts.[46] Treatment of local anaesthetic systemic toxicity depends on the level of severity. Supportive care should be initiated, including oxygen supplementation and manual ventilation if necessary. If the patient is exhibiting signs of seizure activity, a benzodiazepine should be administered. Careful monitoring of the patient's cardiovascular status should be pursued in order to rule out life-threatening cardiac toxicity. Should cardiovascular depression be encountered, judicious use of fluid support and inotropes may be all that is necessary to restore normal cardiovascular parameters. Cardiac arrhythmias should not be treated with further administration of sodium channel blockers.[47] Alternatively, amiodarone is recommended for the management of ventricular arrhythmias associated with local anaesthetic overdose.[47] If cardiac arrest or a malignant ventricular arrhythmia should occur, cardiopulmonary resuscitation should be initiated immediately. Vasopressin and calcium channel blockers should be avoided. Intravenous lipid emulsion has been shown to be effective for treatment of refractory arrhythmias caused by local anaesthetic overdose.[48]

Local Toxicity

Neurotoxicity can result from direct injury to the nerve cells when local anaesthetics are applied.[49] Chondrotoxicity is a common sequela of injection of local anaesthetics into joint spaces,[50] therefore, intraarticular administration is discouraged. Finally, myotoxicity has also been reported after administration of local anaesthetics into skeletal muscle.[51]

Methemoglobinemia

Local anaesthetics have the potential to cause oxidative damage to haemoglobin, resulting in the formation of methaemoglobin. Benzocaine and prilocaine are the agents most commonly associated with the development of methemoglobinemia.[52]

Drug interactions

Local anaesthetics potentiate the effects of non-depolarizing muscle relaxants. Simultaneous administration of succinylcholine and ester local anaesthetics, both metabolized by pseudocholinesterase's, may potentiate the effect of each other. Cimetidine and propranolol decrease hepatic blood flow and amide local anaesthetic clearance increasing the potential for systemic toxicity. Opioids and alpha-2 adrenergic agonists potentiate the effects of local anaesthetics and vice versa.

Special Preparations

Lidocaine Patches

Lidocaine patches were introduced in human medicine in the early 1990s and approved in 1999 by the US Food and Drug Administration (FDA) for the treatment of neuropathic pain caused by herpes zoster, commonly known as shingles.[53] Since then, they have been used in humans for chronic low back pain,[54-56] osteoarthritis,[57] painful idiopathic distal sensory polyneuropathy,[58] focal neuropathic pain in patients with cancer,[59] myofascial pain syndrome,[60] and diabetic polyneuropathy.[61] Lidocaine patches have also been used to treat pain after surgical procedures,[62-64] and to provide pre-emptive analgesia.[65] The lidocaine patch (Lidoderm) is made of a nonwoven polyester felt backing containing adhesive material, and 5% lidocaine (50 mg of lidocaine per gram of adhesive with 700 mg of lidocaine per patch). A release liner protects the adhesive site of the patch and has to be removed before application. The patch is an occlusive delivery system that rehydrates the skin by preventing water loss. The hydration of the stratum corneum enhances the absorption of the drugs through the skin itself.[66] Lidoderm comes in sealed packaging as a nonsterile 10 by 14 cm patch and can be cut to the desired size before application.

In humans, a decrease in pain without numbness or loss of normal sensitivity to temperature and touch of the area where the patch is applied is described.[67] It has been shown that the systemic absorption of lidocaine is minimal, even when an extended dosage regimen is used,[68] suggesting that the analgesic effect is due to the topical absorption. The exact mechanism of action is unknown. It is likely that the amount of lidocaine that penetrates the skin is sufficient to block only sodium channels of small and damaged nociceptors but not enough to block the A-ß sensory filaments. The blockade of these channels prevents movement of sodium intracellularly, which stabilizes the nerve fibre membranes and stops the action potential responsible for transduction and transmission of nociception.[69]

In veterinary medicine, lidocaine patches have been used to treat postoperative pain for several surgical procedures, such as laparotomies, thoracotomies, hemilaminectomies, stifle surgery, total ear canal ablations, and amputations.[70,72] The patch is applied at the end of the procedure after skin closure. Because the

patch is not sterile, it is recommended either to place sterile gauzes over the incision or to cut the patch and apply it around the surgical wound. The lidocaine patch is self-adhesive; however, the protective liner has to be removed and the skin has to be cleaned before application. A surgical film or a bandage can be used to cover and protect the patch and the surgical site. Based on clinical experience and pharmacokinetic data, recommendations on the number of patches per kilogram have been published.[72] Unfortunately, the clinical efficacy of lidocaine patches used for postoperative pain management in dogs is not supported by published data and no clinical studies have been conducted in cats. Two studies in dogs undergoing hemilaminectomies and ovariohysterectomy concluded that the lidocaine patch did not provide additional analgesia compared with the control group.[70,71]

Liposomal Bupivacaine

Exparel is an extended-release formulation of bupivacaine approved in 2011 by the FDA for postsurgical analgesia in humans and sold by Pacira Pharmaceuticals. In this formulation, the bupivacaine is contained in numerous aqueous chambers separated from each other by lipid membranes. The bilayer structure of these membranes consists of phospholipids, triglycerides, and cholesterol. The chambers containing bupivacaine are combined to form microscopic spherical liposomes with a multivesicular, nonconcentric honeycomb-like structure. With time, the vesicles slowly break down, causing the release of bupivacaine and reorganization of the lipid membrane of the liposomes.[73,74] Two multicentric, double-blind, randomized, placebo-controlled studies were conducted as part of the FDA approval process.[75,76] The investigators showed that liposomal bupivacaine provided extended pain relief superior to placebo up to 48 hours after bunionectomy,[75] and 72 hours after haemorrhoidectomy.[76] Both clinical trials reported that the subjects in the treatment group used less opioid postoperatively and adverse effects were considered mild and less frequent than in the placebo group.[75,76] After the approval, Exparel has been used extensively in human medicine for a variety of soft tissue and orthopaedic surgeries. A randomized, double-blind, active-control study compared the efficacy of the liposomal bupivacaine to bupivacaine hydrogen chloride (HCl) mixed with epinephrine for bilateral, cosmetic, submuscular augmentation mammaplasty.[77]

Although the study was underpowered, there was a trend of better analgesia and decreased opioid consumption in the prolonged release bupivacaine group. Another study was conducted in adult subjects undergoing open colectomy.[78] The investigator reported that, when liposomal bupivacaine based multimodal analgesic regimen was used for postoperative analgesia, opioid consumption, hospitalization time, and costs decreased. Khalil and colleagues.[79] compared Exparel administered via intercostal block versus standard continuous thoracic epidural for analgesia after thoracotomies. Subjects receiving the intercostal block reported lower pain scores at day 1 and 3 and had a slightly lower average hospital length of stay. The efficacy of liposome-encapsulated bupivacaine administered via ultrasound guided transversus abdominis plane (TAP) block has been evaluated in subjects undergoing abdominal surgery.[80-83] Most of the human literature on liposomal bupivacaine used for orthopaedic procedures is focused on postsurgical analgesia for total knee arthroplasty (TKA).[84-90] The results published for these studies are controversial. A randomized, multicentre, parallel-group, double-blind, dose-ranging study showed that periarticular liposomal bupivacaine provided greater analgesia while subjects were at rest compared with bupivacaine HCl. However, no differences were found in pain during activity, opioid consumption, and resumption to normal daily activity.[85] No difference in pain scores and narcotic use was found in 2 prospective studies in which Exparel was compared with bupivacaine HCl.[90] and a modified Ranawat suspension (ropivacaine, epinephrine, ketorolac, and clonidine).[86] administered via periarticular injection. Similar results were published by Pichler and colleagues.[89] in a retrospective cohort study. The investigators concluded that liposomal bupivacaine did not decrease inpatient opioid prescriptions and opioid-related complications. Liposomal bupivacaine seems to have an equal or better safety profile than bupivacaine HCl.

The incidence of adverse events is low when recommended doses are administered and the incidence of these side effects is lower when compared with bupivacaine HCl.[91,92] The most common adverse effects are nausea, constipation, and vomiting. Tachycardia and bradycardia have also been reported; however, these were considered mild to moderate in severity and did not require any therapeutic interventions.[92] ECGs and cardiovascular adverse events were evaluated in a phase 2, randomized, double-blind, dose-ranging study of liposomal bupivacaine. In the same report, the investigators analysed data from 4 phase 1 studies in which either ECG or Holter monitor findings were assessed. The results showed no cardiac adverse effects.[93] Although several studies have been published on liposomal bupivacaine in dogs,[94-96,97] Currently, no studies have been published on the use of Nocita in cats. As part of the FDA approval process, Aratana Therapeutics conducted 2 studies, 1 on effectiveness and the other to assess the safety profile in cats.[98]

Liposomal bupivacaine has the potential of becoming 1 of the few options for managing postsurgical pain currently when the availability of opioid drugs is becoming alarmingly limited. Although it has been used experimentally via different block modalities, only local tissue infiltration for cranial cruciate ligament surgery in dogs and peripheral nerve block for onychectomy in cats has been approved. Further clinical trials are needed to assess the efficacy and safety of this formulation

administered via different routes and for different surgical procedures in veterinary medicine.

Future Directions in Local Anesthetic Research

An area of significant interest currently in our field, is the antimetastatic potential of the local anaesthetics particularly the IV lidocaine infusion due possibly to effects from its systemic absorption. The concept that IV lidocaine infusions may have a role in the perioperative management of cancer patients is extremely important as it impacts millions of patient's worlds- wide and warrants further investigation. There is a plethora of in vitro studies but sparse in vivo evidence from preclinical trials that have shown the antimetastatic properties of local anaesthetics.[99] Mechanisms involved in this process, to mention a few, include molecules such as Src Kinase and the Intracellular Adhesion Molecule (ICAM),[100] the sodium channels,[101] processes such antiproliferative effects,[102] and DNA demethylation.[103] The focus of immediate future research is to conduct proof of concept human studies that elucidate mechanisms by which IV lidocaine infusions may affect the biology of cancer and then proceed with multicentre randomised control studies to evaluate the effect of those infusions on cancer recurrence.

CONCLUSION

Local anaesthetics act on nerve endings or around nerve trunks, reversibly blocking the generation and conduction of sensory nerve impulses, and temporarily eliminating local sensation under the condition of consciousness, which are suitable for local surgical operation as well as treatment. Herein, we mainly reviewed the, Local anaesthetics are the only drugs that can fully block nociception by blocking the action potentials within neurons via inhibition of voltage-gated sodium channels. They are weak bases, with a molecular weight ranging from 220 to 288 Da. Lidocaine can be administered systemically to provide analgesia, anti-inflammatory effects, antiarrhythmic effects, and reduction in inhalant anaesthetic requirements, and to enhance gastrointestinal motility and free-radical scavenging. Lidocaine patches are used in veterinary medicine for postoperative pain; however, published data do not support their use. Liposomal bupivacaine is an extended-release formulation that can provide pain relief up to 72 hours after administration.

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REFERANCES

1. A. Brown, R. Weiss, C. Greenberg, et al., Interscalene blockfor shoulder arthroscopy: comparison with general anesthesia, Arthroscopy, 1993; 9(3): 295–300.
2. G. Weinberg, T. VadeBoncouer, G. Ramaraju, et al., Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats, Anesthesiology, 1998; 88(4): 1071–1075.
3. G. Weinberg, R. Ripper, D. Feinstein, et al., Lipid emulsion infusion rescues dogs from bupivacaine-induced cardiac toxicity, Reg. Anesth. Pain Med., 2003; 28(3): 198–199.
4. J. Picard and T. Meek, Lipid emulsion to treat overdose of local anaesthetic: the gi of the glob, Anaesthesia, 2006; 61(2): 107–109.
5. M. Rosenblatt, M. Abel, G. Fischer, et al., Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest, Anesthesiology, 2006; 105(1): 217–225.
6. R. Litz, M. Popp, S. Stehr, et al., Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion, Anaesthesia, 2006; 61(8): 800–801.
7. G. Cave and M. Harvey, Intravenous lipid emulsion as antidote beyond local anesthetic toxicity: a systematic review, Acad. Emerg. Med., 2009; 16(9): 815–824.
8. A. Sirianni, K. Osterhoudt, D. Calello, et al., Use of lipid emulsion in the resuscitation of a patient with prolonged cardiovascular collapse after overdose of bupropion and lamotrigine, Acad. Emerg. Med., 2008; 51(4): 412–415.
9. M. Harvey and G. Cave, Intralipid outperforms sodium bicarbonate in a rabbit model of clomipramine toxicity, Acad. Emerg. Med., 2007; 49(2): 178–185.
10. M. Harvey, G. Cave, K. Hoggett, et al., Correlation of plasma and peritoneal diasylate clomipramine concentration with hemodynamic recovery after intralipid infusion in rabbits, Acad. Emerg. Med., 2009; 16(2), 151–156.
11. D. Crandell and G. Weinberg, Moxidectin toxicosis in a puppy successfully treated with intravenous lipids, J. Vet. Emerg. Crit. Care, 2009; 19(2): 181–186.
12. S. Kampe, M. Warm, S. Kasper, et al., Concept for postoperative analgesia after pedicled TRAM flaps: Continuous wound instillation with 0.2% ropivacaine via multilumen catheters. A report of two cases, Br. J. Plast. Surg., 2003; 56(5): 478–483.
13. L. Nielsen, P. Lumholt and L. Halmich, Local anaesthesia with vasoconstrictor is safe to use in areas with endarteries in ngers, toes, noses and ears, Ugeskr. Laeg., 2014; 176(44): 44.
14. S. Gy¨orke and V. Lukyanenko, Dual effects of tetracaine on spontaneous sodium release in rat ventricular myocytes, J. Physiol., 1997; 500(2): 297–309.
15. S. Derry, P. Wiffen, R. Moore, et al., Topical lidocaine for neuropathic pain in adults, Cochrane Database Syst. Rev., 2014; 7: CD010958.

16. A. Mart´ı, D. Simancas, V. Anand, et al., Prophylactic lidocaine for myocardial infarction, Cochrane Database Syst. Rev., 2015; 8: CD008553.
17. L. Slaughter, A. Patel and J. Slaughter, Pharmacological treatment of neonatal seizures: a systematic review, J. Child Neurol., 2013; 28(3): 351–364.
18. R. Morabito, A. Marino, S. Dossena, et al., Nematocyst\ discharge in Pelagia noctiluca (Cnidaria, Scyphozoa) oral arms can be affected by lidocaine, ethanol, ammonia and acetic acid, Toxicon, 2014; 83: 52–58.
19. M. Segal, G. Rogers, H. Needleman, et al., Hypokalemic sensory overstimulation, J. Child Neurol., 2007; 22(12): 1408–1410.
20. D. Jackson, A. Chen and C. Bennett, Identifying true lidocaine allergy, J. Am. Dent. Assoc., 1994; 125(10): 1362–1366.
21. J. Picard, S. Ward, R. Zumpe, et al., Guidelines and the adoption of 'lipid rescue' therapy for local anaesthetic toxicity, Anaesthesia, 2009; 64(2): 122–125.
22. A. Gulihar, S. Robati, H. Twaij, et al., Articular cartilage and local anaesthetic: A systematic review of the current literature, J. Orthop., 2015; 12: S200–S210.
23. W. A. Carterall, Molecular mechanisms of gating and drug block of sodium channels, Sodium Channels and Neuronal Hyperexcitability, Novartis Foundation Symposia, 2001; 241: 206–225.
24. S. Sheu and W. Lederer, Lidocaine's negative inotropic and antiarrhythmic actions. Dependence on shortening of action potential duration and reduction of intracellular sodium activity, Circ. Res., 1985; 57(4): 578–590.
25. K. Collinsworth, S. Kalman and D. Harrison, The clinical pharmacology of lidocaine as an antiarrhythymic drug, Circulation, 1974; 50(6): 1217–1230.
26. A. Pupka, J. Sikora, J. Mauricz, et al., The usage of synthol in the body building, Polim. Med., 2009; 39(1): 63–65.
27. N. Bernardo, M. Siqueira, M. DePaiva, et al., Caffeine and other adulterants in seizures of street cocaine in Brazil, Int. J. Drug Policy, 2003; 14(4): 331–334.
28. A. Gargiulo, G. Burns and C. Huck, Dyclonine hydrochloridea topical agent for managing pain, Ill. Dent. J., 1992; 61(4): 303–304.
29. J. Schmidt, L. Blockus and R. Richards, The Pharmacology of Pramoxine Hydrochloride: A New Topical Local Anesthetic, Curr. Res. Anesth. Analg., 1953; 32(61): 418–425.
30. Cousins MJ, Bridenbaugh PO, Carr DB, et al. Cousins and Bridenbaugh's neural blockade in clinical anesthesia and pain medicine 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2009.
31. Narahashi T, Frazier DT. Site of action and active form of local anesthetics. Neurosci Res (N Y), 1971; 4: 65–99.
32. Butterworth JFT, Strichartz GR. Molecular mechanisms of local anesthesia: a review. Anesthesiology, 1990; 72(4): 711–34.
33. Gissen AJ, Covino BG, Gregus J. Differential sensitivity of fast and slow fibers in mammalian nerve. II. Margin of safety for nerve transmission. Anesth Analg, 1982; 61(7): 561–9.
34. Tucker GT, Boyes RN, Bridenbaugh PO, et al. Binding of anilide-type local anesthetics in human plasma. I. Relationships between binding, physicochemical properties, and anesthetic activity. Anesthesiology, 1970; 33(3): 287–303.
35. Butterworth GR & Strichartz GR. Molecular Mechanisms of Local Anesthesia: A Review. Anesthesiology, 1990; 72(4): 711-734.
36. Becker DE & Kenneth L Reed. Essentials of Local Anesthetic Pharmacology. Anesth Prog, 2006; 53: 98–109.
37. Hollmann MW & Durieux ME. Local anesthetics and the inflammatory response: a new therapeutic indication? Anesthesiology, 2000; 93(3): 858-75.
38. Piegeler T, Votta-Velis EG, Liu G et al. Antimetastatic potential of amide-linked local anesthetics: inhibition of lung adenocarcinoma cell migration and inflammatory Src signaling independent of sodium channel blockade. Anesthesiology, 2012; 117(3): 548-59.
39. Ferrante FM, Paggioli J, Cherukuri S, & Richard AG. The Analgesic Response to Intravenous Lidocaine in the Treatment of Neuropathic Pain. Anesth Analg, 1996; 82(1): 9197.
40. Schwartzman RJ, Patel M, Grothusen JR, & Alexander GM. Efficacy of 5-day continuous lidocaine infusion for the treatment of refractory complex regional pain syndrome. Pain Med, 2009; 10(2): 401-12.
41. Koppert W, Zeck S, Sittl R et al. Low-dose lidocaine suppresses experimentally induced hyperalgesia in humans. Anesthesiology, 1998; 89: 1345-53.
42. Van der Wal SE, van den Heuvel SA, Radema SA et al. The in vitro mechanisms and in vivo efficacy of intravenous lidocaine on the neuroinflammatory response in acute and chronic pain. Eur J Pain, 2016; 20(5): 655-74.
43. Morgan GE, Mikhail MS, Murray MJ: Clinical Anesthesiology, 4th edition. New York, McGraw-Hill, 2006; 263-288.
44. Cox B, Durieux ME, Marcus MA. Toxicity of local anaesthetics. Best Pract Res Clin Anaesthesiol, 2003; 17(1): 111–36.
45. Beecroft C, Davies G. Systemic toxic effects of local anaesthetics. Anaesth Intensive Care Med, 2013; 14(4): 146–8.
46. Aberg G. Toxicological and local anaesthetic effects of optically active isomers of two local

anaesthetic compounds. Acta Pharmacol Toxicol (Copenh), 1972; 31(4): 273–86.
47. Weinberg GL. Current concepts in resuscitation of patients with local anaesthetic cardiac toxicity. Reg Anesth Pain Med, 2002; 27(6): 568–75.
48. Weinberg G, Ripper R, Feinstein DL, et al. Lipid emulsion infusion rescues dogs from bupivacaine-induced cardiac toxicity. Reg Anesth Pain Med, 2003; 28(3): 198–202.
49. Verlinde M, Hollmann MW, Stevens MF, et al. Local anesthetic-induced neurotoxicity. Int J Mol Sci., 2016; 17(3): 339.
50. Baker JF, Mulhall KJ. Local anaesthetics and chondrotoxicty: what is the evidence? Knee Surg Sports Traumatol Arthrosc, 2012; 20(11): 2294–301.
51. Hussain N, McCartney CJL, Neal JM, et al. Local anaesthetic-induced myotoxicity in regional anaesthesia: a systematic review and empirical analysis. Br J Anaesth, 2018; 121(4): 822–41.
52. Davis JA, Greenfield RE, Brewer TG. Benzocaine-induced methemoglobinemia attributed to topical application of the anesthetic in several laboratory animal species. Am J Vet Res., 1993; 54(8): 1322–6.
53. Rowbotham MC, Davies PS, Verkempinck C, et al. Lidocaine patch: double blind controlled study of a new treatment method for post-herpetic neuralgia. Pain, 1996; 65(1): 39–44.
54. Galer BS, Gammaitoni AR, Oleka N, et al. Use of the lidocaine patch 5% in reducing intensity of various pain qualities reported by patients with low-back pain. Curr Med Res Opin, 2004; 20(Suppl 2): S5–12.
55. Gimbel J, Linn R, Hale M, et al. Lidocaine patch treatment in patients with low back pain: results of an open-label, nonrandomized pilot study. Am J Ther., 2005; 12(4): 311–9.
56. Hines R, Keaney D, Moskowitz MH, et al. Use of lidocaine patch 5% for chronic low back pain: a report of four cases. Pain Med, 2002; 3(4): 361–5.
57. Gammaitoni AR, Galer BS, Onawola R, et al. Lidocaine patch 5% and its positive impact on pain qualities in osteoarthritis: results of a pilot 2-week, open-label study using the Neuropathic Pain Scale. Curr Med Res Opin, 2004; 20(Suppl 2): S13–9.
58. Herrmann DN, Barbano RL, Hart-Gouleau S, et al. An open-label study of the lidocaine patch 5% in painful idiopathic sensory polyneuropathy. Pain Med, 2005; 6(5): 379–84.
59. Lopez Ramirez E. Treatment of acute and chronic focal neuropathic pain in cancer patients with lidocaine 5 % patches. A radiation and oncology department experience. Support Care Cancer, 2013; 21(5): 1329–34.
60. Lin YC, Kuan TS, Hsieh PC, et al. Therapeutic effects of lidocaine patch on myofascial pain syndrome of the upper trapezius: a randomized, double-blind, placebo-controlled study. Am J Phys Med Rehabil, 2012; 91(10): 871–82.
61. Barbano RL, Herrmann DN, Hart-Gouleau S, et al. Effectiveness, tolerability, and impact on quality of life of the 5% lidocaine patch in diabetic polyneuropathy.
62. Gilhooly D, McGarvey B, O'Mahony H, et al. Topical lidocaine patch 5% for acute postoperative pain control. BMJ Case Rep, 2011; 2011 [pii:bcr0620103074].
63. Habib AS, Polascik TJ, Weizer AZ, et al. Lidocaine patch for postoperative analgesia after radical retropubic prostatectomy. Anesth Analg, 2009; 108(6): 1950–3.
64. Saber AA, Elgamal MH, Rao AJ, et al. Early experience with lidocaine patch for postoperative pain control after laparoscopic ventral hernia repair. Int J Surg, 2009; 7(1): 36–8.
65. Kim KH. Use of lidocaine patch for percutaneous endoscopic lumbar discectomy. Korean J Pain, 2011; 24(2): 74–80.
66. Riviere JE, Papich MG. Potential and problems of developing transdermal patches for veterinary applications. Adv Drug Deliv Rev, 2001; 50(3): 175–203.
67. Pasero C. Pain control: lidocaine patch 5%. Am J Nurs, 2003; 103: 75–8.
68. Gammaitoni AR, Davis MW. Pharmacokinetics and tolerability of lidocaine patch 5% with extended dosing. Ann Pharmacother, 2002; 36(2): 236–40.
69. Gammaitoni AR, Alvarez NA, Galer BS. Safety and tolerability of the lidocaine patch 5%, a targeted peripheral analgesic: a review of the literature. J Clin Pharmacol, 2003; 43(2): 111–7.
70. Merema DK, Schoenrock EK, Le Boedec K, et al. Effects of a transdermal lidocaine patch on indicators of postoperative pain in dogs undergoing midline ovariohysterectomy. J Am Vet Med Assoc, 2017; 250(10): 1140–7.
71. Re Bravo V, Aprea F, Bhalla RJ, et al. Effect of 5% transdermal lidocaine patches on postoperative analgesia in dogs undergoing hemilaminectomy. J Small Anim Pract, 2018; 60(3): 161–6.
72. Weil AB, Ko J, Inoue T. The use of lidocaine patches. Compend Contin Educ Vet, 2007; 29(4): 208–10, 212, 214-206.
73. Lascelles BDX, Kirkby Shaw K. An extended release local anaesthetic: potential or future use in veterinary surgical patients? Vet Med Sci., 2016; 2(4): 229–38.
74. Simone A. Center for drug evaluation and research, clinical review NDA 022-496 Exparel (bupivacaine). Food and Drug Administration (FDA). 2011. Availble at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011 /022496Orig1s000 MedR.pdf. Accessed January 10, 2019.
75. Golf M, Daniels SE, Onel E. A phase 3, randomized, placebo-controlled trial of DepoFoam_ bupivacaine (extended-release

bupivacaine local analgesic) in bunionectomy. Adv Ther., 2011; 28(9): 776–88.
76. Gorfine SR, Onel E, Patou G, et al. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial. Dis Colon Rectum, 2011; 54(12): 1552–9.
77. Smoot JD, Bergese SD, Onel E, et al. The efficacy and safety of DepoFoam bupivacaine in patients undergoing bilateral, cosmetic, submuscular augmentation mammaplasty: a randomized, double-blind, active-control study. Aesthet Surg J., 2012; 32(1): 69–76.
78. Cohen SM. Extended pain relief trial utilizing infiltration of Exparel (@), a longacting multivesicular liposome formulation of bupivacaine: a Phase IV health economic trial in adult patients undergoing open colectomy. J Pain Res., 2012; 5: 567–72.
79. Khalil KG, Boutrous ML, Irani AD, et al. Operative intercostal nerve blocks with long-acting bupivacaine liposome for pain control after thoracotomy. Ann Thorac Surg., 2015; 100(6): 2013–8.
80. Feierman DE, Kronenfeld M, Gupta PM, et al. Liposomal bupivacaine infiltration into the transversus abdominis plane for postsurgical analgesia in open abdominal umbilical hernia repair: results from a cohort of 13 patients. J Pain Res., 2014; 7: 477–82.
81. Felling DR, Jackson MW, Ferraro J, et al. Liposomal bupivacaine transversus abdominis plane block versus epidural analgesia in a colon and rectal surgery enhanced recovery pathway: a randomized clinical trial. Dis Colon Rectum, 2018; 61(10): 1196–204.
82. Keller DS, Tahilramani RN, Flores-Gonzalez JR, et al. Pilot study of a novel pain management strategy: evaluating the impact on patient outcomes. Surg Endosc, 2016; 30(6): 2192–8.
83. Stokes AL, Adhikary SD, Quintili A, et al. Liposomal bupivacaine use in transversus abdominis plane blocks reduce pain and postoperative intravenous opioid requirement after colorectal surgery. Dis Colon Rectum, 2017; 60(2): 170–7.
84. Bagsby DT, Ireland PH, Meneghini RM. Liposomal bupivacaine versus traditional periarticular injection for pain control after total knee arthroplasty. J Arthroplasty, 2014; 29(8): 1687–90.
85. Bramlett K, Onel E, Viscusi ER, et al. A randomized, double-blind, dose-ranging study comparing wound infiltration of DepoFoam bupivacaine, an extendedrelease liposomal bupivacaine, to bupivacaine HCl for postsurgical analgesia in total knee arthroplasty. Knee, 2012; 19(5): 530–6.
86. Collis PN, Hunter AM, Vaughn MD, et al. Periarticular injection after total knee arthroplasty using liposomal bupivacaine vs a modified ranawat suspension: a prospective, randomized study. J Arthroplasty, 2016; 31(3): 633–6.
87. Hadzic A, Minkowitz HS, Melson TI, et al. Liposome bupivacaine femoral nerve block for postsurgical analgesia after total knee arthroplasty. Anesthesiology, 2016; 124(6): 1372–83.
88. Hyland SJ, Deliberato DG, Fada RA, et al. Liposomal bupivacaine versus standard periarticular injection in total knee arthroplasty with regional anesthesia: a prospective randomized controlled trial. J Arthroplasty, 2019; 34(3): 488–94.
89. Pichler L, Poeran J, Zubizarreta N, et al. Liposomal bupivacaine does not reduce inpatient opioid prescription or related complications after knee arthroplasty: a database analysis. Anesthesiology, 2018; 129(4): 689–99.
90. Schroer WC, Diesfeld PG, LeMarr AR, et al. Does extended-release liposomal bupivacaine better control pain than bupivacaine after total knee arthroplasty (TKA)? A prospective, randomized clinical trial. J Arthroplasty, 2015; 30(9 Suppl): 64–7.
91. Portillo J, Kamar N, Melibary S, et al. Safety of liposome extended-release bupivacaine for postoperative pain control. Front Pharmacol, 2014; 5: 90.
92. Viscusi ER, Sinatra R, Onel E, et al. The safety of liposome bupivacaine, a novel local analgesic formulation. Clin J Pain, 2014; 30(2): 102–10.
93. Bergese SD, Onel E, Morren M, et al. Bupivacaine extended-release liposome injection exhibits a favorable cardiac safety profile. Reg Anesth Pain Med, 2012; 37(2): 145–51.
94. Richard BM, Ott LR, Haan D, et al. The safety and tolerability evaluation of DepoFoam bupivacaine (bupivacaine extended-release liposome injection) administered by incision wound infiltration in rabbits and dogs. Expert Opin Investig Drugs, 2011; 20(10): 1327–41.
95. Richard BM, Newton P, Ott LR, et al. The safety of exparel _ (bupivacaine liposome injectable suspension) administered by peripheral nerve block in rabbits and dogs. J Drug Deliv, 2012; 2012: 962101.
96. Richard BM, Rickert DE, Newton PE, et al. Safety evaluation of Exparel (Depo- Foam bupivacaine) administered by repeated subcutaneous injection in rabbits and dogs: species comparison. J Drug Deliv, 2011; 2011: 467429.
97. Lascelles BD, Rausch-Derra LC, Wofford JA, et al. Pilot, randomized, placebo controlled clinical field study to evaluate the effectiveness of bupivacaine liposome injectable suspension for the provision of post-surgical analgesia in dogs undergoing stifle surgery. BMC Vet Res., 2016; 12(1): 168.

98. Nocita (bupivacaine liposome injectable suspension) [package insert]. Leawood (KS): Aratana Therapeutics, Inc, 2018.
99. Missair A, Cata JP, Votta-Velis G et al. Working Group on the Impact of Perioperative Pain Management and Anesthesia on Cancer Recurrence. Regional Anesth Pain Med, 2018. (in press).
100. Piegeler T, Votta-Velis EG, Liu G et al. Antimetastatic potential of amide-linked local anesthetics: inhibition of lung adenocarcinoma cell migration and inflammatory Src signaling independent of sodium channel blockade. Anesthesiology, 2012; 117(3): 548-59.
101. Onkal R & Djamgoz MD. Molecular pharmacology of voltage-gated sodium channel expression in metastatic disease: clinical potential of neonatal Nav1.5 in breast cancer. Eur J Pharmacol, 2009; 625(1-3): 206-219.
102. Lucchinetti E, Awad AE, Rahman M et al. Antiproliferative effects of local anesthetics on mesenchymal stem cells: potential implications for tumor spreading and wound healing. Anesthesiology, 2012; 116(4): 841-856.
103. Lirk P, Berger R, Hollman MW, & Fiegl H. Lidocaine time- and dose-dependently demethylates deoxyribonucleic acid in breast cancer cell lines in vitro. Br J Anaesth, 2012; 109(2): 200-207.