

Potentially desirable secondary effects of local anesthetics

Efeitos secundários potencialmente desejáveis dos anestésicos locais

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ABSTRACT

Despite the use of local anesthetics (LAs) having the primary purpose of producing nerve blockages by the inhibition of Na⁺ channels, the literature has shown that these agents may have additional pharmacological actions, also affecting the potassium and calcium channels and acting on intracellular mechanisms. Besides causing anesthesia, the LAs may act directly on other receptors and their signaling pathways which are involved in processes of inflammation, platelet activation, nociception, peripheral pain and arrhythmias, among others, increasingly seeking better clinical efficacy and safety, in addition to new and potentially useful properties for the LAs. Therefore, the aim of this study is to search the scientific literature and review the pharmacology and the additional potentially desirable effects of the LAs used in medical clinic.

Keywords: Local Anesthetics/pharmacology, Sodium Channels, Literature Review by Topic

RESUMO

Apesar do uso dos anestésicos locais (ALs) ter a finalidade principal de produzir bloqueios nervosos pela inibição dos canais de Na⁺, a literatura tem mostrado que esses agentes podem ter ações farmacológicas adicionais, afetando também, os canais de potássio e de cálcio e agindo em mecanismos intracelulares. Os ALs podem, além de causar anestesia, agir diretamente sobre outros receptores e suas vias de sinalização que estão envolvidos nos processos de inflamação, ativação plaquetária, nocicepção, dor periférica e arritmias, dentre outras, buscando cada vez mais, uma melhor eficácia e segurança clínica, além de novas e potencialmente úteis propriedades para os ALs. Assim, o objetivo deste estudo foi pesquisar em literatura científica e descrever uma revisão da farmacologia e dos efeitos adicionais potencialmente desejáveis dos principais anestésicos locais usados na clínica médica.

Palavras-chave: Anestésicos Locais/farmacologia, Canais de Sódio, Literatura de Revisão como Assunto

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INTRODUCTION

The first local anesthetic (LA), discovered by chance in the 19th century was cocaine. Albert Niemann was the first to isolate cocaine in 1860. Later, Sigmund Freud studied its physiological actions and Carl Koller introduced cocaine into clinical practice, in 1884, as an anesthetic for topical use in ophthalmologic surgeries. Due to its toxicity and addictive properties, research for the discovery of synthetic substitutes was initiated, resulting in the synthesis of procaine, which became the prototype for all the LAs for about half a century. In 1943, lidocaine was synthesized, thus originating the class of aminoamides.¹

The action mechanism of the LAs is connected to the reversible blockage of the Na⁺ channels dependent on voltage, impeding the influx of Na⁺ necessary to initiate and propagate the action potentials, maintaining the cell in a state of rest. Local anesthetic acts by paralyzing the peripheral sensory nerve endings, or by interrupting the transmission of sensitivity to pain between the nerve endings (nociceptors) and the encephalon. These agents can also affect the potassium and calcium channels and act in intracellular mechanisms.²

The LAs, in general, are weak bases, with pK_a values of around 8 or 9, which is why they are partially ionized in the physiological pH. In their structure they present an ester or amide link, which leads to a higher or lower susceptibility to metabolic hydrolysis. Drugs containing the ester function, procaine for example, are normally inactive in the plasma or tissues by esterases.³ Drugs containing the amide function are more stable and generally have a longer half-life.^{4,5}

The desirable characteristics for an anesthetic molecule include, aside from a reversible action of long duration and the selectivity between being a sensory block and a motor block, the reduction of local or systemic toxicity. In addition it cannot be an irritant to the tissues or cause permanent damage to the nerve structures.⁶

In recent decades, new studies have revealed other potentially desirable effects of LAs, aside from the effects of anesthesia, showing a promising future for this class of compounds.

METHOD

The strategy of bibliographical search was carried out using the following data bases: Pubmed, Medline, the Bireme base (Virtual Library on

health), Scopus and the Cochrane Library, in addition to didactic books. All years available were researched, by means of the following relevant phrases and key words: Local anesthetics, side effects of local anesthetics, secondary effects of LAs, lidocaine, procaine, bupivacaine, ropivacaine, and uses for local anesthetics.

Undesirable effects of LAs

LAs interfere with the function of various organs in which nerve impulses occur. The main toxic effects of LAs come from systemic absorption subsequent to regional administration, and can lead to neurotoxicity and/or cardiotoxicity. LAs can stimulate the CNS causing agitation, jitters, and tremors. High concentrations can trigger CNS depression and respiratory insufficiency, leading to death. Cardiac toxicity is characterized by a reduction in electrical excitability, conduction, strength, and myocardial contraction. LAs depress intestinal contractions and also relax the smooth vascular and bronchial muscles. They also affect the transmission at the neuromuscular junction. Therefore the risk of toxicity can be minimized according to the following premises: I) use the lowest concentration possible, if necessary, dilute; ii) avoid injection directly into the intravascular space; iii) use epinephrine to reduce absorption of the LA by the bloodstream thereby prolonging the anesthetic effects; iv) modify the dosage for patients with greater risk of systemic toxicity.^{1,7,4}

Lidocaine (Xylocaine, Lignocaine)

Lidocaine represents the prototypical amide-class LA. It produces anesthesia more quickly and intensely than an equal concentration of procaine. Its sympathetic-colytic actions in addition to its anesthetic action can replace procaine for patients who have contra-indications to derivatives of the *p*-amino-benzoic acid group (PABA) or esters, but is 50% less vasodilating than procaine. It must not be used in cases of hyper-sensitivity to the amide group, in patients with neurological, cardiac, or hepatic disorders, or with severe arterial hyper- or hypo-tension.

In low concentrations LAs are able to suppress the spontaneous neural discharges responsible for neuropathy. As such they have long been used for the analgesia in diabetic neuropathy, neuralgias, peripheral nerve damages, and sympathetic reflex dystrophy. However, in spite of their effectiveness in treating pain, systematic LAs are limited in use due to adverse reactions from the central nervous system.

The use of topical LA formulations can be an effective alternative for systemic release

systems in the treatment of chronic pain. Such formulations are widely used as topical anesthetics for small surgical procedures and in the treatment of post-herpetic neuralgia (PHN), especially at ages at which the patient is more susceptible to adverse systematic reactions.^{11,12}

Several works describe the efficacy of using topical 5% lidocaine patches in the treatment of PHN. The action mechanism proposed for lidocaine is in reducing the generation and conduction of peripheral nerve impulses through the blockage of the Na⁺ channels in the injured nociceptors situated directly beneath the application.^{12,13,14}

The complex regional pain syndrome (CRPS) can be treated with a regional blocking anesthetic to promote analgesia and enable medical physical rehabilitation. Sympathetic blocking through the use of intravenous lidocaine which, actuating the “wind-up” phenomenon, helps desensitize the affected region, has long been used in the treatment of CRPS.¹⁵

The myofascial pain syndrome (MPS) is one of the most common causes of muscular-skeletal pain. One study was done to compare the effects of lidocaine patches, placebos, and a 5% bupivacaine injection on MPS symptoms in terms of pain, disability, and local tissue hyper sensibility. All pain symptoms were alleviated by using lidocaine patches and the bupivacaine injection when compared with the placebo, emphasizing a preferential therapy with lidocaine patches in patients whose discomfort with the injection was particularly great.¹⁶ It is also known that lidocaine is capable of controlling pain, many times stabbing, in the muscular spasms of dorsalgia.¹⁷

Soft tissue injection with cortical steroids and local anesthetics can bring relief from chronic lumbar pain associated with myofascial syndrome and fibromyalgia.¹⁸ A clinical study was made with 25 patients to demonstrate the initial results obtained using injections of 1% lidocaine without a vasoconstrictor into the trigger points in the treatment of chronic lumbar pain with myofascial origins. The results confirmed the effectiveness of the technique on chronic lumbar pain that showed resistance to other forms of treatment, emphasizing the deactivation of the trigger points as an efficient therapeutic modality.¹⁹

EMLA cream (2.5% lidocaine + 2.5% prilocaine) is one of the best known topical formulations containing lidocaine. It provides the maximum benefit when applied with a plaster, to improve absorption, in 30-60 minutes. EMLA is often used for skin anesthesia for small vascular procedures and superficial laser treatments.^{20,21}

The cream ELA-Max is marketed in Brazil under the name Dermomax (4% lidocaine) and is also a topical formulation very commonly used for temporary relief of pain associated with small cuts that only affect the epidermis, small burns (first degree), irritations, and insect bites. It is also used before procedures such as venipuncture or intradermal, subcutaneous, or intramuscular injections, or laser skin treatment. It is a topical anesthetic with a technology that enhances the skin's absorption of the product and promotes the rapid onset of action with a prolonged effect. The medicine enables the dispersion of active substances thanks to multi-layered phospholipid spheres that mimic cutaneous lipids and incorporate themselves into the corneal extract of the skin.^{22,23}

Another pharmaceutical form used in the treatment of PHN is a measured-dosage spray of 8% lidocaine (Xylocaine pump spray[®], XPS). Double-blind random clinical testing against a placebo was performed on patients with PHN wherein 79% felt satisfied with the therapy due to immediate pain relief, lack of adverse systemic reactions, and the convenience of using a spray.²⁴ The same lidocaine spray was successfully used in a clinical test in the treatment of post-traumatic peripheral neuropathy, resulting in a reduction in the visual analog scale for continuous pain.²⁵

Anti-arrhythmic drugs constitute the main therapy in suppression of atrial fibrillation. The class I of these anti-arrhythmia drugs are generally local anesthetics, which act on the nerve membranes and myocardium by reducing the inhibiting conduction to the zero phase of the potential of action. Intravenous lidocaine is specifically indicated in ventricular arrhythmia related to myocardial ischemia.^{26,27} Adverse reactions include vomiting and convulsions that predominantly involve the CNS and the heart.²⁸

Various studies have demonstrated the synergistic interaction of local anesthetics with neuromuscular blockers (NMB) *in vitro* and *in vivo* by venous and epidural means.^{29,30} The association of a NMB and a local anesthetic results in an enhancement of the neuromuscular blocking effects. Cardoso et al³¹ described the effects of lidocaine on the pharmacodynamics of rocuronium, an NMB indicated in situations where rapid tracheal intubation may be necessary. In this study, lidocaine administered prior to the rocuronium was not able to speed the onset of this NMB's action, but prolonged its pharmacological duration without extending the time for complete recovery of neuromuscular function.

One alternative for the use of lidocaine is based on its neuroprotecting effects in cases of cerebral ischemia.³² Lei et al^{33,34} studied the neuroprotecting effects of small doses (10 µmol/L) of lidocaine in a cerebral ischemia model using rats and concluded that pretreatment with the LA significantly reduce the amount of ischemic necrosis, improved the neurological results, and inhibited post-ischemic weight loss. In spite the good results in animal models, tests on humans are still necessary for future inclusion into clinical practice.

Among the other anti-inflammatory and anti-coagulant drugs tested, lidocaine showed the best results as far as diminishing the incidence of neurological decompression sickness in a test on rats, having a better chance of success in a support therapy for this disease.³⁵

Various studies have shown that using an intravenous infusion of lidocaine diminishes the duration of hospitalization and improves analgesia and post-operative gastro-intestinal motility (after ileal surgery). The anti-inflammatory action of lidocaine could be the mechanism responsible for these beneficial effects.^{36,37}

LAs also show antiviral activity as described in various works. One controlled double-blind study against a placebo in patients with herpes simplex virus showed good results with a topical application of a lidocaine/prilocaine cream. This treatment resulted in a 50% reduction of the symptoms and eruptions resulting from the viral infection.^{38,39}

Procaine (Novocaine)

Introduced in 1905, procaine was the first injecting synthetic LA. These days it is only used for infiltrations in soft tissue, blocking trigger points and mesotherapy. Procaine can be used as an alternative LA in cases of allergic reactions to the LAs of the amide group.^{40,41}

Procaine is used in penicillin G preparations because the peak serum concentration of the penicillin G declines rapidly after intramuscular injection owing to its half life being only 30 minutes. With procaine, penicillin G is released slowly from the injection site and produces low but continuous concentrations of the antibiotic into the body, and can be found in the muscle up to even five days after the injection. The presence of procaine also makes the injection less painful due to its anesthetic effect.^{42,43}

Infiltrations with 0.5% procaine are an efficient therapeutic resource in cases of MPS. The use of procaine is justified by its advantage of giving a rapid effect and by its lower level of local muscular toxicity. Also, the lower concentration of anesthetic reduces the risk of adverse systemic reactions.^{44,45}

Jin et al described a study concerning the development of new formulations of procaine in a gel with appropriate bioadhesive properties. Different permeability enhancers were studied such as glycooids and non-ionic surfactants in an attempt to optimize the speed of skin permeation. The procaine gel containing oleo-ethers of polyoxyethylene showed twice the analgesic activity compared to the control, emphasizing the efficacy of using enhancers in bioadhesive formulations of Las' gels.⁴⁶

Procaine and its derivatives have also been studied as anti-cancer agents acting by inhibiting DNA methyltransferase and inhibiting the growth of cancerous breast cells. Various works have emphasized procaine as a promising future anti-cancer therapy based on epigenetics.⁴⁷⁻⁴⁹ Procaine hydrochloride has been shown to increase anti-tumor activity as well as reduce the nephro- and hemo-toxicity of cisplatin, a drug often used in the treatment of ovarian and testicular carcinomas in tests on rats. The protective and enhancing effects of procaine and its metabolites can be attributed to their direct and indirect effects on the pharmacokinetics and pharmacodynamics of cisplatin.⁵⁰ The antitumor activity of a hydrochloride complex of platinum (DPR) formed between procaine and cisplatin is also described. This study suggests that DPR acts by inducing apoptosis and exhibits a selective mechanism of action against two types of tumors, neuroblastoma and SCLC (small-cell lung cancer). Despite being a monofunctional platinum compound, DPR is capable of forming a bifunctional adduct for the liberation of procaine residue.^{51,52}

When mixed with other medicines, procaine diminishes vascular absorption and increases the half-life, permitting rapid, complete, and prolonged diffusion of medicines despite its anesthetic potential being only one fifth that of lidocaine and its length of action being very short. Even though the efficacy of a product within a local pathology is a function of its length of time near the injury, procaine can be considered an effective therapeutic vector. It is much less toxic than the majority of lidocaines.⁵³ All these characteristics probably make procaine an attractive drug in the meso-therapeutic method.^{17,54}

Bupivacaine (Marcaine, Sensorcaine)

Bupivacaine is available for clinical use in its enantiomeric racemic form. The S enantiomer, levobupivacaine (Chirocaine), is less cardiotoxic and seems to have less anesthetic potency. Its use is described for epidural, caudal,

and spinal anesthesia, also for peripheral nerve blocks, for ophthalmic and dental anesthesia, in varying pediatric applications, and regional intravenous anesthesia.⁵⁵

The LAs most widely used in the treatment of chronic and acute pain are of the aminoamide type. Bupivacaine is a potent anesthetic capable of producing prolonged anesthesia. This characteristic, along with its tendency to provide more sensory blockage than motor, makes it a popular drug for prolonged analgesia in the post-operative period.^{42,56}

Various authors have described the substantial reduction of post-operative laparoscopic cholecystectomy with the use of local intra-peritoneal anesthesia.⁵⁷⁻⁵⁹ In one of these clinical trials, 0.5% levobupivacaine was administered to pre-surgical patients, resulting in a significant diminution of pain and the need for opioid, thereby emphasizing the efficacy and safety of the technique.⁵⁹

Local anesthetics can be used intra-articularly to prevent pain after arthroscopic knee surgery in a therapy of pre-emptive analgesia, which permits attenuation or prevention of central sensitization induced by the surgery.^{60,61} Nonetheless, the duration of the analgesia furnished by these anesthetics is short and the patients may need an analgesic with opioids.⁶² Elsharnouby et al⁶³ studied the influence of adding magnesium sulphate, an antagonist of the N-methyl-D-aspartate (NMDA) receptors, to the intra-articular bupivacaine injection in post-surgical patients in an attempt to improve and prolong the analgesia induced by this local anesthetic. It is known that the NMDA receptors located along the peripheral and visceral pain pathways play an important role in nociception. This study reveals a better post-operative analgesia with bupivacaine-magnesium sulphate in comparison with the placebo.⁶⁵

Clonidine, an adrenergic α_2 antagonist, is added to intrathecal LAs to improve intra-operative analgesia and to increase the duration of the sensory and motor blockage. It enhances the effects of the opioid and LAs, acting on the receptors coupled with the K^+ channels, increasing the extracellular conductance of K^+ .^{66,67}

A study seeking to distinguish the efficacy of the analgesic properties of levobupivacaine alone or in combination with clonidine,⁶⁸ when administered as an epidural infusion was made for the treatment of post-operative pain in hip-replacement patients. The therapy with the combination of the two drugs was well tolerated and presented better analgesia than that using the LA alone.⁶⁹

Taking into account that the desirable characteristics of an LA are long-lasting action, selectivity, and low local and/or systemic toxicity, one successful alternative these days is a modified release, through the formation of inclusion complexes with cyclodextrins or liposomes.^{70,71} Moraes et al⁷¹ described a study concerning the formation of inclusion complexes of levobupivacaine with cyclodextrins, emphasizing the release and characterization of these complexes. This work showed that the complexation of LAs causes changes in the properties of the medicine such as increased solubility and modification of the release profile.

Bupivacaine forms stable structures with DNA plasmids encapsulated in liposomes. Within these structures, the DNA is protected from degradation by the nuclease. Intramuscular and intradermal administration of the DNA-bupivacaine mixtures generate a better immune response than with using DNA alone. The bupivacaine-DNA complex serves as a DNA liberation system in vaccines and gene therapy.^{72,73}

Some LAs, including lidocaine, tetracaine, prilocaine, and bupivacaine have the capacity to inhibit the growth of *Candida albicans*. One study with lidocaine and bupivacaine showed that these agents present a fungistatic action at low concentrations due to metabolic damage to the fungus, while at higher concentrations, they present fungicidal action due to direct damage to the cytoplasmic membrane.⁷⁴

Ropivacaine (Naropin)

Ropivacaine and levobupivacaine are two long-acting LAs recently introduced to the market. Ropivacaine has a moderate onset, long duration, conduction blockage, and significant separation between sensory and motor blockage. It was developed as an alternative to bupivacaine and, by being an isomerically pure compound, appears to present fewer CNS and cardiotoxic effects.⁷⁵ It is useful administered epidurally or by infiltration, and alleviates post-operative pain.^{76,77}

Aside from LAs being used as nerve blockages by inhibiting the Na^+ channels, it has become clear that these agents can have additional therapeutic actions, also affecting potassium and calcium channels and acting in intracellular mechanisms.^{2,78}

The use of anesthesia and analgesia is associated with a significant reduction in the incidence of deep vein thrombosis (DVT) and pulmonary thrombo-embolism (PTE) after orthopedic or urologic surgery. Epidural anesthesia exerts a protecting effect on the coagulation system to prevent a state of

pre-operative hyper-coagulability.⁷⁹ Höne-mann et al demonstrated the inhibition of the thromboxane A_2 signal path (TXA_2) through the use of ropivacaine, bupivacaine, and lidocaine in a recombinant model with interference to the platelet aggregation, which could partially explain the anti-thrombotic actions of the epidural analgesic and venous infusion of LAs.^{79,80}

LAs have also shown anti-inflammatory actions influencing various cellular functions such as phagocytosis and the production of peroxide (hydrogen peroxide??), which are relevant in inflammatory processes.³⁹ In this context, the work done by Blumenthal et al⁸¹ described the anti-inflammatory effects of low and clinically-relevant doses of ropivacaine on neutrophils and pulmonary endothelial and epithelial cells *in vitro* and *in vivo*.

The intravenous administration of LAs is prescribed for patients with bronchial hyper-reactivity as a method for mollifying bronchi-constriction during tracheal intubation. Groeben et al concluded that lidocaine and ropivacaine significantly attenuated bronchi-spasms induced by histamine, emphasizing that other properties of LAs, aside from just their anesthetic effects, were responsible for the attenuation of bronchial hyper-reactivity.^{82,83}

Some studies suggest a microbial activity of the LAs against a wide spectrum of human pathogens. The action mechanism for the anti-bacterial activity has not yet been totally clarified, but it is believed that this activity owes itself to a rupture of the cell membrane, leading to the cell components spilling out and the consequent death of the cell.^{84,85} The anti-bacterial effects do not depend solely on the length of the LA's alkyl chain, but also on the chemical configuration of the compound, representing a greater potency for the *R* isomer. This is why ropivacaine, a pure *S* isomer, presents less anti-bacterial activity than the other LAs such as bupivacaine and lidocaine.⁸⁶

CONCLUSION

LAs present a variety of pharmacological activities, not only the local anesthesia by inhibition of the Na^+ channels, but also by action at other receptor sites and intracellular mechanisms. In spite of the great interest in the scientific community in these alternative therapeutic actions, many studies have been conducted only in animal models, further limiting the additional uses of these compounds in other

pathologies. Thus, more clinical trials on humans are necessary before the implementation of alternative therapies with LAs.

The search for better clinical efficacy and safety, as well as new and potentially useful properties of LAs, should be the objective of future research into this class of compounds.

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