ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Update on local anesthetics hypersensitivity reactions

Atualização em reações de hipersensibilidade aos anestésicos locais

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ABSTRACT

Local anesthetics are essential in many medical and dental procedures. They work by stabilizing neuronal membranes and inhibiting the transmission of neural impulses, which allows these procedures to be performed more safely and without pain. Adverse drug reactions are defined by the World Health Organization as all harmful, unintended and undesirable effects of a medication, which occur at doses used for prevention, diagnosis and treatment. Hypersensitivity reactions are unpredictable type B adverse reactions that clinically resemble allergic reactions and may or may not involve an immune mechanism. True hypersensitivity reactions to local anesthetics are rare, although overestimated. In this review, we highlight the need for a thorough evaluation of patients with suspected allergic reaction to local anesthetics, including investigation of other possible allergens that may have been used in the procedure, such as analgesics, antibiotics and latex. The investigation strategy and patient selection for testing should be based on clinical history. In this way, we will be able to provide more assertive and safe guidelines to patients.

Keywords: Local anesthetics, esters, amides, drug hypersensitivity, lidocaine.

RESUMO

Os anestésicos locais são essenciais em diversos procedimentos médicos e odontológicos. Funcionam estabilizando as membranas neuronais e inibindo a transmissão de impulsos neurais, o que permite a realização desses procedimentos com mais segurança e sem dor. As reações adversas a drogas são definidas pela Organização Mundial da Saúde como todos os efeitos nocivos, não intencionais e indesejáveis de uma medicação, que ocorrem em doses usadas para prevenção, diagnóstico e tratamento. As reações de hipersensibilidade são reações adversas do tipo B, imprevisíveis, que clinicamente se assemelham a reações alérgicas e podem ou não envolver um mecanismo imune. As reações de hipersensibilidade verdadeiras aos anestésicos locais são raras, apesar de superestimadas. Nesta revisão destacamos a necessidade de uma avaliação completa dos pacientes com suspeita de reação alérgica aos anestésicos locais, incluindo a investigação de outros possíveis alérgenos que tenham sido utilizados no procedimento, como analgésicos, antibióticos e látex. A estratégia de investigação e seleção de pacientes para testes deve se basear na história clínica. Dessa forma, poderemos fornecer orientações mais assertivas e seguras aos pacientes.

Descritores: Anestésicos locais, ésteres, amidas, hipersensibilidade a drogas, lidocaína.

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Submitted: 09/05/2021, accepted: 12/04/2021.

Arq Asma Alerg Imunol. 2022;6(1):63-70.

http://dx.doi.org/10.5935/2526-5393.20220005

Introduction

Therelief, control and blocking of pain was one of the most important advances in Medicine and a huge leap forward for humanity. Today, there are numerous procedures that benefit from the use of local anesthetics (LA), substances that block sensory, motor and autonomic functions without causing unconsciousness.[1]

The use of local anesthetics dates back to the most ancient civilizations, when the Incas chewed coca leaves to obtain a feeling of well-being. Cocaine itself was isolated in 1860 by the work of the medical student Albert Niemann and Professor Frederick Woller, but its practical use as an anesthetic in isolation only happened years later, with the studies of Carl Koller, on its effects on the eye, and Sigmund Freud about the stimulating effects of this substance on the brain. Since then, several safe LAs have been synthesized, some of which are no longer used because they have serious toxic effects on the cardiovascular and nervous systems.[2]

It is estimated that the Adverse reactions to LA occur between 2.5 to 10% of patients exposed to this class of drugs, but hypersensitivity reactions are rare and described in less than 1% of cases of adverse reactions.[3]

Hypersensitivity reactions to local anesthetics can initially be divided into *local* or *systemic*, and this distinction is important in investigation. According to the time of onset of signs and symptoms, but also considering the clinical manifestations, we can classify reactions into immediate (installation of signs and symptoms within an hour, and may occur up to 6 hours) and late (after an hour, up to days or weeks).[4]

Taking into account the rarity of allergic hypersensitivity reactions to LA, the difficulty in clarifying the real mechanism causing the reaction and the fear of health professionals and the patient himself to perform a new procedure in the event of an adverse event with the use of LA, it is necessary to carry out the investigation protocol through skin and provocation tests. Such tests help in the identification and confirmation of possible suspected agents, in order to know the real prevalence of LA allergy, and also to rule out the diagnosis or provide other alternative LAs for use.[5]

Therefore, in this review, made from searches for original articles, reviews, guidelines and consensus in the MEDLINE and Latin American and Caribbean Literature on Health Sciences (LILACS) databases, using the terms: *local anesthetics hypersensitivity*, *local anesthetics adverse effects*, *pharmacology*, *diagnostic tests*, we updated the prevalence of reactions to LA, discussed the pharmacology of these medications, described the characteristics of each type of reaction and ended with the indications and investigation protocol, and consequently the outcomes of their results.

Pharmacology of local anesthetics

LA are the only class of drugs capable of completely blocking the arrival of nociceptive impulses to the cerebral cortex, thus preventing the perception of these stimuli by the patient.[6]

Lidocaine was synthesized in 1948 for topical use or intravenous infusion, and since then new drugs have been created, varying their characteristics in terms of onset time, duration of action and potential toxicity.[6]

The LA molecule is composed of three parts: a lipophilic aromatic ring, an ester or amide ligand, and an amino terminus (Figure 1).[7,8]

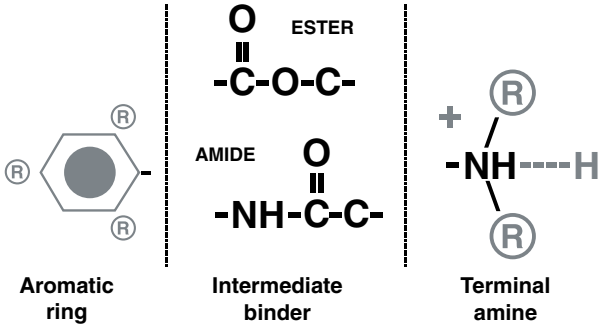


Figure 1
Chemical structure of local anesthetics

The amine functional group and its branches are linked to the aromatic ring by an intermediate ester or amide chain, which will determine the metabolic mechanism of each LA. This is important, as amide-type local anesthetics are chemically more stable, have a lower risk of allergic reactions, and have a longer

half-life due to their hepatic degradation, compared to the ester group, which is primarily metabolized by plasma cholinesterase.[7]

Cross-reactivity between drugs of the ester group is frequent due to the common metabolite of this group, para-aminobenzoic acid (PABA). The amide group LAs generally do not cross-react with each other, but there are some case reports of such reactions. Between the ester and amide groups there is no cross-reactivity.[9,10] Table 1 presents the commonly used LAs.

Table 1
Local anesthetics

Group 1 (Esters)	Group 2 (Amides)
Benzocaine	Lidocaine
Cocaine	Mepivacaine
Procaine	Prilocaine
Proparacaine	Articaine
Chloroprocaine	Bupivacaine
Tetracaine	Levobupivacaine
	Ropivacaine

Four physicochemical properties determine the activity of local anesthetics: pKa (dissociation constant in a solution, that is, it defines the pH at which the drug forms will be in equilibrium: 50% ionized and 50% non-ionized), molecular weight, lipid solubility and degree of protein binding.[6,11]

In general, local anesthetics with low pKa will have a faster onset of action, as they have a lower degree of ionization at physiological pH, that is, it is through the non-ionized form that the drug diffuses through the neural membrane and then into the cell, establishes its ionized or active form, binding to the intracellular sodium channel to exert its function. Molecular weight is inversely related to the tissue diffusion capacity of LA.[6]

The molecular structure, with the presence of the aromatic ring and its ramifications, is the main determinant of the solubility of this class of drugs. LA with greater lipid solubility present greater diffusion through the neural membrane, and, therefore, the greater the potency of these drugs. However, LA with higher lipid solubilities are absorbed more slowly, as this physicochemical property can influence the dispersion of these drugs through tissue fluids, as well as the commercial concentrations in which they are formulated.[6]

The degree of protein binding determines the free fraction of the drug available to bind to target receptors, so the duration of drug action is directly related to the protein binding capacity of the local anesthetic.[12]

The LA mechanism of action is based on blocking the transmission of action potentials within neurons through the inhibition of voltage-gated sodium channels. When at rest, the channels are closed, opening when depolarized and soon after entering an inactive state, in order to facilitate repolarization of the nerve cell membrane. Thus, when LA binds to sodium channels, its inactive state inhibits the action potential in nerve fibers, generating favorable conditions for drug binding, therefore, the stimulation of nerve fibers facilitates the onset of its effects.[6,11]

Nerve fiber blockage occurs gradually with the onset of loss of sensitivity to pain, temperature, touch, proprioception, and, eventually, skeletal muscle tone. Thus, individuals can still feel the touch when the pain is already absent.[12]

In pharmacokinetic terms, it is observed that LA are absorbed according to the site of administration, determined by its lipid solubility, vascularization of the site of action and the presence or absence of a vasoconstrictor incorporated into the solution.[6]

Regarding the use of vasoconstrictors in the solution, their presence reduces the systemic absorption of the anesthetic, which consequently remains for a longer time at the administration site. Other factors that can influence the maximum plasma concentration are the amount of drug, the patient's cardiac output, and vasodilation at the neural blockade site.[6]

Regarding the distribution of LA, those of the amino amide type are better distributed due to their slower metabolism than the amino esters, and both have renal excretion.[6]

Hypersensitivity reactions to local anesthetics

Hypersensitivity reactions are unpredictable, dose-independent, type B adverse reactions that relate to individual predisposition and clinically resemble allergic reactions. They may have an immunological mechanism not involved in their pathogenesis, being classified as allergic and non-allergic, respectively.[13]

The vast majority of reactions to LA are not allergic hypersensitivity reactions and involve other mechanisms, such as those listed below.[14]

- Toxic: occurs by accidental intravascular administration or in high doses of LA and has symptoms such as tremors, agitation, arrhythmia, hypotension, drowsiness, nausea, vomiting, apnea, excitement, convulsion and myocardial dysfunction.
- Psychosomatic: related to anxiety or fear, include symptoms such as hyperventilation (tachypnea and dyspnea), paresthesias, palpitation, tachycardia, nausea, dizziness and sweating.
- Vasovagal: bradycardia and pallor.
- Pharmacological effect of vasopressors: palpitation, tachycardia, tremors, headache and increased blood pressure.
- Idiosyncrasies: methemoglobinemia related to the administration of higher doses of LA, especially prilocaine.

LAs are used both in injectable form and in topical preparations, and can lead to a wide variety of manifestations. Differentiating the allergic process from the non-allergic process is not always easy, as the history is generally imprecise, the drug involved is unknown, the signs and symptoms are very varied, transient and most of the time do not require treatment.[9,15] The presence of generalized skin symptoms and hypotension related to the use of LA has been described as a predictor of positive skin tests or provocation.[5]

The ester group LAs are the most associated with allergic hypersensitivity reactions, and their active metabolite and potential allergenic epitope is paraminobenzoic acid (PABA).[9] The cross-reactivity between the LAs of the ester group is attributed to this common metabolite. PABA has in its structure components similar to parabens (methylparabens, propylparabens), found in makeup, sunscreens and creams. Regarding LA of the amide group, the metaxylene component is the possible allergenic epitope and may be present in other drugs such as antiretrovirals, antiarrhythmics and antidiarrheals.[16,17] Therefore, both groups of LA can lead to an allergic hypersensitivity reaction already in the first exposure to the drug due to primary sensitization by cross-reactivity.[17]

Two types of allergic reactions to LA are recognized: the *immediate* IgE-mediated reactions (type I), characterized by the release of histamine and other mediators, and the *delayed* reactions, mediated by the T cell (type IV).

Immediate reactions correspond to less than 1% of hypersensitivity reactions, typically occur within 1 hour of LA administration and present as urticaria, angioedema, pruritus, bronchospasm and anaphylaxis.[5,18] The severity of the reaction depends on the allergen dose, route of administration and the amount of specific IgE. In case of suspected anaphylaxis, tryptase dosage may be useful in the diagnosis.[18]

Late reactions are more frequent, observed in 2.4 to 4.1% of patients.[19] They can be local or systemic. Local reactions occur within hours or even days after topical application or subcutaneous/submucosal injections of LA, and may persist for several days. They are characterized by allergic contact dermatitis or edema and local erythema, similar to cellulitis. Contact dermatitis typically presents with eczema, blistering, blistering, and oozing. Late-onset edema at the LA injection site may or may not accompany contact dermatitis, and when it affects mucosa it leads to blistering and scaling.[20] In addition to LA from the benzocaine ester group, cinchocaine is often identified as a contact allergen. Late systemic reactions may present with generalized skin eruptions, such as maculopapular rash.[20]

Differential diagnosis of hypersensitivity reactions to local anesthetics

Adverse reactions most commonly confused with hypersensitivity reactions include syncope, panic attacks and toxic effects due to inadvertent intravascular drug administration.[20,21]

Possible differential diagnoses and their symptoms are listed below.

Allergy to other agents

Allergic reactions involving local anesthetic preparations may be due to other constituents of the injection solution than the drug itself. Excipients such as preservatives (eg benzoates - used in multidose vials) and antioxidants (eg metabisulfites - used in local anesthetics in a solution containing adrenaline) can cause hypersensitivity reactions.[21] Historically, the most sensitizing components in local anesthetic solutions were preservatives such as methylparabens, used in plastic anesthetic tubes to prevent losses

due to microbiological contaminants. However, LA used in Dentistry are single-use items, which do not require the inclusion of parabens. There are varying concentrations of methylparaben in plastic tubes, although they do not have an indication on their package insert. Considering the presence of methylparaben, glass tubes are safer. Since the amount of methylparaben is not specified on the packaging, and is not regulated by the National Health Surveillance Agency, it is important to alert professionals about its presence.

Latex allergy

Latex contained in rubber tampons, natural rubber gloves and other dental materials should also be considered.[22]

Psychogenic reactions

Psychogenic reactions are one of the most common adverse reactions associated with the use of local anesthetics in dentistry. They can manifest in many ways, with syncope being the most common, but other symptoms include panic attacks, hyperventilation, nausea, vomiting, and changes in heart rate or blood pressure, which can cause pallor. These reactions can be misdiagnosed as allergic reactions and can also mimic them with signs such as reddening of the skin, rash with red spots, swelling, and bronchospasm. All patients have some degree of autonomic response to injections, ranging from mild tachycardia and sweating to syncope.[22]

Toxic reactions

Toxic reactions can occur if high levels of anesthetic enter the bloodstream. Local anesthetics can reach the circulation as a result of repeated injections, inadvertent intravascular administration, or overdose in patients who have problems eliminating or metabolizing these drugs. Toxic side effects are predominantly neurological and include excitability or agitation, sedation, dizziness, slurred speech, mood change, diplopia, disorientation, and muscle spasms. Higher blood levels can result in tremors, respiratory depression and seizures.[22]

Vasoconstrictor agents such as adrenaline can also cause adverse effects. Adrenaline toxicity can result in symptoms such as anxiety, restlessness, tremors, throbbing headache, palpitations, sweating, pallor, weakness, dizziness and tachypnea.[22] Toxic reactions can be minimized when using correct doses of anesthetic and safe injection techniques.[22]

Prevention of adverse effects

When the patient experiences signs and symptoms that are suggestive of an allergic reaction, possible alternative causes should be considered, such as contact with other common allergens, toxic dose, or a psychogenic reaction. Possible causes of the symptoms experienced should be discussed with the patient. The use of the terms “allergic” and “allergy” should be avoided when discussing any adverse event.[22]

Adverse reactions caused by toxicity or anxiety can be minimized by:[22]

– administering injections with an aspiration syringe to avoid intravascular injection;
– in nervous patients, use relaxants to relieve anxiety. For extremely anxious patients, sedation may be necessary;
– treating patients in the supine position to prevent fainting;
– give injections slowly to reduce discomfort and improve solution location;
– restrict the total dose of anesthetic given to the patient to prevent the occurrence of toxic effects from overdose. The maximum dose for the patient can be calculated using the dosage information contained in the package insert and literature data, always taking into account the patient's age and weight, any concomitant drug therapy and underlying medical conditions.

Diagnostic methods and flowchart

All patients with a clinical history suggestive of an allergic hypersensitivity reaction to LA should be evaluated and submitted to the completion of the European Network for Drug Allergy (ENDA) questionnaire. Based on this information, the analysis of indication of tests for investigation is carried out.[23,24]

When an allergic reaction to drugs is suspected, the initial strategy is to immediately discontinue the drug and after 4 to 6 weeks the investigation can be carried out through skin tests, such as: patch test, prick test or puncture followed by the test. intradermal (ID) and provocation tests, always based on clinical history and risk stratification.[25] In this interval, it is possible

to exclude the used LA and release some alternative based on cross-reactivity to local anesthetics.

Several studies have evaluated the application of investigation protocols for LA. A retrospective Danish study evaluated 189 provocation tests performed in patients with suspected immediate allergic reaction to LA, none of which had a positive result.[19] Another retrospective evaluation in Germany excluded LA allergy in patients with a history suggestive of anaphylaxis. 771 subcutaneous provocations were performed with a positive result in only two cases, evidencing the predictive value of the negative ID test in investigations of these drugs.[14] Kallan et al. showed a frequency of only 3.52% of positive tests for local anesthetics in a sample of 398 patients, totaling 452 provocations performed.[5]

In Brazil, Aun et al. performed a retrospective study at the Medication Allergy Ambulatory at the University of São Paulo, evaluating 93 provocation tests with LA in patients with a history of immediate hypersensitivity to these drugs and obtained three positive results, one of them in the prick test.[26] Tanno et al. studied 33 patients with a history of reaction during or after (up to 24 hours) a procedure in which LA was used. All provocation tests had negative results, and two patients had a positive puncture test for latex, which were also confirmed with specific IgE dosage.[8] In a study carried out at a Brazilian reference center (UNIFESP), five patients had a history of skin reactions (urticaria and angioedema) or anaphylaxis after the use of local anesthetics in dental procedures. In the investigation, no patient was positive to the skin tests and challenged with the suspected drugs or therapeutic option (LA of the amide class, without vasoconstrictor).[27]

Therefore, according to reports in the literature, allergic reactions to LA are rare, and another suspected agent should always be investigated concomitantly, such as antimicrobials and latex.[9,24]

Allergic reactions to latex can present with immediate symptoms (hives, angioedema, sneezing, wheezing, and anaphylaxis) or delayed symptoms (eczema). The investigation should be carried out especially in risk groups such as atopics, healthcare professionals and other workers exposed to latex, patients undergoing multiple surgeries, children with urogenital malformations or spina bifida, and those with a history of perioperative anaphylaxis. Initially, a thorough clinical history should be taken, following a specialized questionnaire for latex allergy. Diagnosis is based on skin tests with standardized extract (93% sensitivity and 100% specificity), latex-specific IgE dosage (80% sensitivity and specificity > 95%) and, in case of a suggestive history and negative tests, provocation tests can be performed. Despite being effective, provocation tests are of high risk for triggering anaphylaxis, being reserved for inconclusive cases.[28]

Regarding reactions to LA, these are usually immediate reactions, and mostly caused by the toxicity of the drug or the associated vasoconstrictor. Thus, the medication often ends up being suspended without a real need, limiting the therapeutic options of patients.[14]

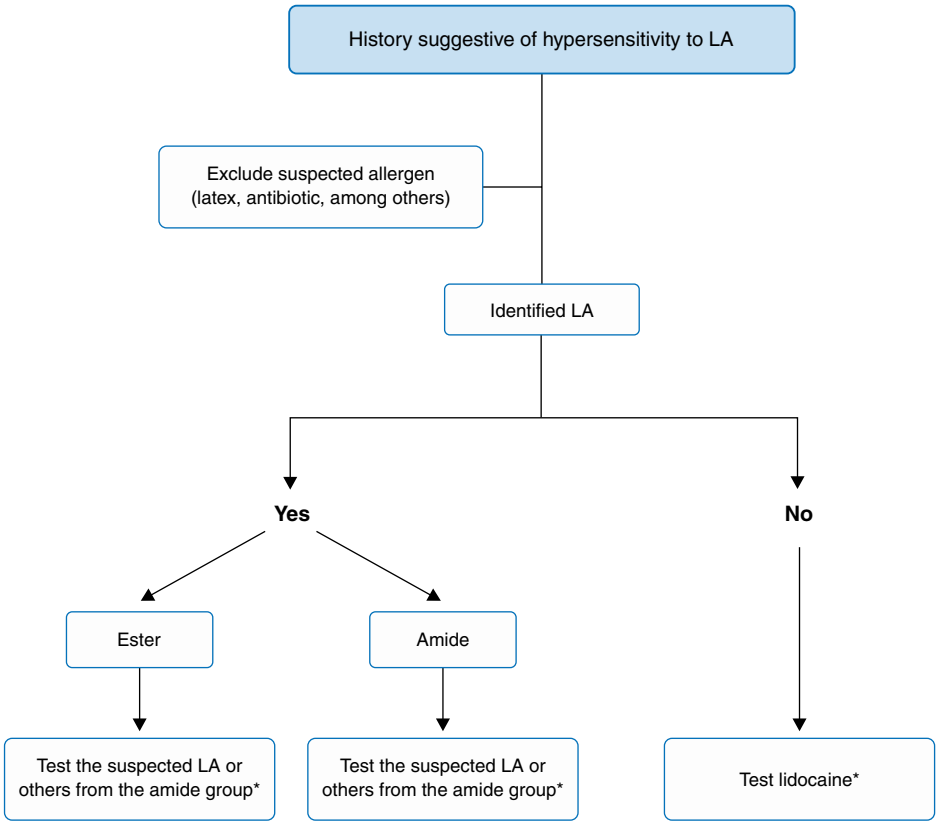
Before starting the investigation, some data about the reaction should be considered: type of procedure performed at the time of reaction, administration of the local anesthetic in relation to the appearance of signs and symptoms, complete review of the reaction mechanism, classification, amount and the concentration of the local anesthetic used, whether the LA contained a vasoconstrictor and the patient's previous pathological history, particularly renal, hepatic, cardiac and psychiatric history.[9]

The LA to be tested must not contain a vasoconstrictor, as this agent may inhibit the formation of papules during the procedure, leading to false-negative results or adverse events associated with its use.[29,30]

The choice of test type should be based on the Gell and Coombs reaction mechanisms, with immediate reading skin tests and provocation tests indicated for investigation of type I reactions and the patch test for type IV reactions.[31] It is essential to obtain the Free and Informed Consent Form (ICF) before performing the tests.

The concentrations of medications for performing skin tests are: prick test with pure LA, ID 1/1032 and patch test with pure medication.[4,33] If the skin test is negative, the investigation is continued by performing the provocation test with 2 mL of pure local anesthetic without vasoconstrictor, subcutaneously, keeping the patient under clinical observation for at least one hour after application.[8]

The drug provocation test is considered the gold standard in the investigation of drug allergy, and should be performed in a controlled environment and with a trained team.[34] Through the CFM resolution nº 2153/2016, the services that perform puncture tests, immunotherapy, intradermal test, desensitization and antigen provocation test were categorized



LA = Local anesthetics

* All skin tests must be performed with LA without a vasoconstrictor. If impossible to peform skin tests and provocation, due to the low risk of cross-reactivity, ester class anesthetics should be replaced by the amide class, and those of the amide class must be replaced by other local anesthetic of the amide class.

Figure 2
Flowchart for investigation of allergy to local anesthetics

as group 3, requiring supplies and equipment (automatic external defibrillator-AED, oxygen source, oropharyngeal cannulas, manual ventilator) for the treatment of emergencies such as anaphylaxis and cardiorespiratory arrest.

Conclusion

True hypersensitivity reactions to LA are rare, but they are quite frequent complaints in Allergology offices. Differential diagnosis with toxic, psychogenic reactions or by other agents such as latex is essential. Research through a detailed anamnesis can be very useful. The type of clinical manifestation, chronology of events and the need for drug treatment to reverse the reaction should be characterized. If the reaction is suggestive of allergic hypersensitivity, immediate and delayed reading skin tests may be used. The SC provocation test is the last step of the diagnostic investigation and must be performed by trained professionals, in an environment with support for reversal of an eventual anaphylactic reaction. Thus, after the entire procedure, the patient can be advised about the type of reaction presented and which LAs are safe for future use.

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No conflicts of interest declared concerning the publication of this article.

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