

Anaphylactic Shock to Lidocaine: A Rare Case Report with Evaluation of Cross-Reactivity among Local Anesthetics

Barradas Lopes J, Reis Ferreira A, João Sousa M, Cadinha S

Allergy and Clinical Immunology Department, Centro Hospitalar de Vila Nova de Gaia/ Espinho, EPE.

Corresponding author:

joanabarradaslopes@gmail.com

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Local anesthetics (LAs) have been widely used to prevent and relieve pain in surgical procedures [1]. Despite its frequent use, IgE-mediated hypersensitivity reactions (HR) to LA are extremely rare and estimated to be <1% [1–3].

The majority of adverse reactions to LAs are non-immunologically mediated and usually occur in relation to procedural trauma, psychomotor responses or due to other substances administered concomitantly as additives or preservatives [3,4].

LAs agents are classified as amides or esters, based on their chemical structure. Since the prevalence of true IgE-mediated HR to LAs is low, little is known about cross-reactivity among these drugs, particularly within the amide group. Case reports have shown different spectrums of tolerance, adding complexity to the task of understanding cross-reactivity patterns [4–9].

We report the case of a 43-year-old caucasian man with a well-controlled NSAIDs-exacerbated respiratory disease, submitted to a routine nasal endoscopy aimed at monitoring nasal polyposis. Few minutes after 2 pulverizations (20mg) of intranasal lidocaine (Xylocaína® Spray), generalized erythema, rhinoconjunctivitis, dyspnea, cough, vomiting, dizziness with hypotension, tachycardia and hypoxemia occurred. Intramuscular adrenaline was administered, followed by intravenous fluid therapy, clemastine, methylprednisolone, salbutamol and oxygen therapy. Symptoms improved, with hypotension and oxygenation recovery. About 1 hour later, hypotension recurred requiring readministration of adrenaline. Blood pressure improved and stabilized, but atrial fibrillation was documented. This led to the administration of digoxin, which reverted the atrial fibrillation in a few

hours. Serum tryptase was 24 ug/L (basal of 4.9 ug/L). The patient had reported no reaction to lidocaine in previous uses. He was discharged 24 hours later and referred to our drug department.

Skin tests and basophil activation test (BAT) were performed with lidocaine and all LAs from the amide group available at our center, namely mepivacaine, articaine and ropivacaine, in order to assess cross-reactivity.

The lidocaine (Lidocaine Braun[®]) and ropivacaine (Ropivacaine Krabi[®]) formulations used were preservative-free. Mepivacaine (Scandinibsa[®]) and articaine (Artinibsa[®]) formulations had preservatives (sodium metabisulphite in both and methylparaben in mepivacaine).

Undiluted formulations for SPT and dilutions of 1/10 for IDT were used, according to ENDA group recommendations. As our patient had a severe anaphylactic reaction, IDT were initially performed with lower concentrations progressing to the maximum non irritative concentration (1/1000-1/10). A positive SPT was defined by a mean diameter of wheal ≥ 3 mm than negative control and positive IDT by an increment of ≥ 3 mm than the initial wheal. BAT was considered positive when activation was $>5\%$ and stimulation index (SI) >2 , in at least one concentration.

SPT with lidocaine 10mg/mL and 20mg/mL were both positive (8.5mm;10mm) (see Figure E1 in the Online Repository). SPT was positive to mepivacaine 30mg/mL (12mm) (Figure 1). SPT and IDT with articaine and ropivacaine were both negative (articaine 40mg/mL for SPT and 0.04-4mg/mL for IDT; ropivacaine 2mg/mL for SPT and 0.2mg/mL for IDT) (Figure 1). BAT was negative for all LAs tested: lidocaine, mepivacaine and articaine.

A placebo controlled subcutaneous challenge with articaine was performed in the intensive care unit. A four step protocol was used, starting with 1/100 of the cumulative dose (40.4mg) and no reaction occurred. Since the reaction with lidocaine was severe and not much is known about cross-reactivity between amide type LAs, we decided to perform a rechallenge with articaine using a two-step

protocol, one week after the first challenge, to assess if the patient had been sensitized in our procedure. No reactions occurred. Drug challenge with ropivacaine was proposed, but the patient decided to postpone further investigation.

We report a rare case of a patient with a severe immediate HR to intranasal lidocaine, with possible cross-reactivity to mepivacaine, but not articaine which the patient subsequently tolerated. We were not able to confirm the tolerance to ropivacaine.

Although the measurements of IgE to lidocaine and other LAs were not available, the clinical history and diagnostic work-up favors an IgE-mediated mechanism, since our patient had an anaphylactic shock and positive SPT to lidocaine and mepivacaine.

The diagnostic work-up in patients with suspected HR to LA is no different from other drugs and includes a detailed clinical history, skin tests and drug challenge [2].

Optimal concentrations for skin tests are well established for LAs, with a negative predictive value of up to 97% [10]. In this patient, skin tests were useful for establishing a diagnosis of HR to lidocaine and to evaluate cross-reactivity between amide type LAs, allowing a safe introduction of an alternative amide type LA. Drug challenge is required to confirm HR when skin tests are negative and it was essential to confirm tolerance to articaine in our patient. BAT to LAs is not standardized, so inconsistencies between BAT and skin tests may occur.

We would like to highlight that, although some of the LAs formulations used had preservatives, HR to them were ruled out because: (i) the lidocaine formulation used to perform skin tests was preservative-free; (ii) the mepivacaine and articaine formulations used contained sodium metabisulphite, and the later was tolerated.

Even though true IgE-mediated HR to LAs is extremely rare, not much is known about cross-reactivity between LAs and the scarce supporting evidence is based on very few case reports[4–9]. If HR is confirmed, tolerance to alternative LAs must be evaluated in order to safely introduce them. Like our patient, most of the few published cases report cross-reactivity between lidocaine and mepivacaine[4,5,7,9],and only one reports tolerance [5]. Data regarding cross-reactivity between lidocaine and articaine is even scarcer[7,8].

In conclusion, although extremely rare, immediate HR to LAs with a putative IgE-mediated mechanism can occur. Skin tests are useful in the diagnosis of these reactions, as well as to help identifying alternative LAs. Existing literature shows a variation in cross-reactivity between amide group LAs, but additional cases must be reported to better advance our understanding.

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Conflict of Interest

The authors have no conflict of interests.

References

1. Bhole M V, Manson AL, Seneviratne SL, Misbah SA. IgE-mediated allergy to local

anaesthetics: Separating fact from perception: A UK perspective. *Br J Anaesth* [Internet]. 2012;108(6):903–11. Available from: <http://dx.doi.org/10.1093/bja/aes162>

2. Garvey LH, Ebo DG, Mertes PM, Dewachter P, Garcez T, Kopac P, et al. An EAACI position paper on the investigation of perioperative immediate hypersensitivity reactions. *Allergy Eur J Allergy Clin Immunol*. 2019;74(10):1872–84.
3. Kvisselgaard AD, Mosbech HF, Fransson S, Garvey LH. Risk of Immediate-Type Allergy to Local Anesthetics Is Overestimated—Results from 5 Years of Provocation Testing in a Danish Allergy Clinic. *J Allergy Clin Immunol Pract* [Internet]. 2018;6(4):1217–23. Available from: <https://doi.org/10.1016/j.jaip.2017.08.010>
4. Fuzier R, Lapeyre-Mestre M, Mertes P, Nicolas J, Benoit Y, Didier A, et al. Immediate- and delayed-type allergic reactions to amide local anesthetics: clinical features and skin testing. *Pharmacoepidemiol Drug Saf*. 2009;18:595–601.
5. Al-Dosary K, Al-Qahtani A, Alangari A. Anaphylaxis to lidocaine with tolerance to articaine in a 12 year old girl. *Saudi Pharm J* [Internet]. 2014;22(3):280–2. Available from: <http://dx.doi.org/10.1016/j.jsps.2013.10.001>
6. Prieto A, Herrero T, Rubio M, Tornero P, Baeza ML, Velloso A, et al. Urticaria due to mepivacaine with tolerance to lidocaine and bupivacaine. *Allergy Eur J Allergy Clin Immunol*. 2005;60(2):261–2.
7. Cuesta-Herranz J, De Las Heras M, Fernández M, Lluch M, Figueredo E, Umpierrez A, et al. Allergic reaction caused by local anesthetic agents belonging to the amide group. *J Allergy Clin Immunol*. 1997;99(3):427–8.
8. Morais-Almeida M, Gaspar A, Marinho S, Rosado-Pinto J. Allergy to local anesthetics of the amide group with tolerance to procaine. *Allergy*. 2003;58:827–8.

9. González-Delgado P, Antón R, Soriano V, Zapater P, Niveiro E. Cross-reactivity among amide-type local anesthetics in a case of allergy to mepivacaine. *J Investig Allergol Clin Immunol*. 2006;16(5):311–3.
10. McClimon B, Rank M, Li J. The predictive value of skin testing in the diagnosis of local anesthetic allergy. *Allergy Asthma Proc* [Internet]. 2011;32(2):95–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21439161>

Tables and figures

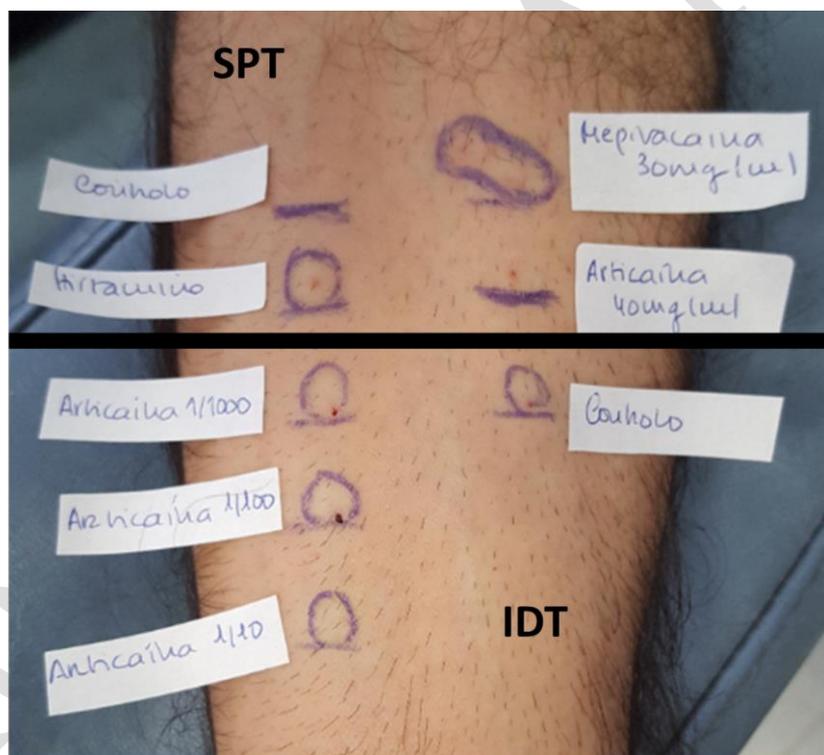


Figure 1: Results of SPT and IDT to mepivacaine and articaine.