Meta-xylene: identification of a new antigenic entity in hypersensitivity reactions to local anesthetics

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Clinical Implications

- The authors report a patient who presented delayed hypersensitivity reactions to several local anesthetics, all containing a meta-xylene entity, but not to articaine, which is a thiophene derivative. Meta-xylene could be the immunogenic epitope.

TO THE EDITOR:

Hypersensitivity reactions to local anesthetics (LAs) are rare and represent less than 1% of all adverse reactions to LAs. Two types of allergic reactions to LAs are recognized: IgE-mediated type 1 reactions and T-cell-mediated type 4 reactions. Type 1 reactions are usually observed within minutes and are characterized by the release of histamine and other mediators, inducing systemic symptoms such as urticaria, angioedema, bronchospasm, and cardiovascular depression.[1] Type 4 hypersensitivity reactions are delayed-type reactions, which primarily occur by T-lymphocyte-mediated mechanisms. After skin exposure to the suspected agent, symptoms are typically observed within 12 to 48 hours of exposure in sensitized patients. The most common clinical manifestation is contact dermatitis, presenting as erythema, pruritus, papules, and vesicles.[2]

LAs are chemically composed of 3 parts, including an aromatic ring connected by an ester or amide link to a secondary or tertiary amine function, which allows their classification as an ester (ie, benzocaine, chloroprocaine, cocaine, procaine, or tetracaine) or amide (ie, articaine, bupivacaine, cinchocaine, lidocaine, mepivacaine, prilocaine, or ropivacaine) LA.[1,3] The carboxylic derivatives (carbonyl group linked to a heteroatom) adopt opposite orientations in ester and amide LAs (Figure 1).

Consequently, ester LAs are more frequently involved in allergic reactions[1] because hydrolysis by plasmatic esterases produces p-aminobenzoic acid (PABA) metabolites that are highly antigenic.[3] Allergic reactions to amide LAs are less frequent due to the lack of PABA formation, and it is generally accepted that cross-reactivity between esters and amides does not occur because their breakdown products differ.[1]

Allergic reactions to both ester and amide LAs are very rare.[4] We report here the case of a patient who presented delayed hypersensitivity reactions to parabens and several amide LAs (lidocaine, mepivacaine, and bupivacaine) but not to articaine. The aromatic ring contained in most LAs is meta-xylene, whereas in articaine, it is a thiophene derivative (Figure 1).[5] Our hypothesis is that the common antigenic determinant in the present case of hypersensitivity to both PABA derivatives and amide LAs could be meta-xylene. The patient gave his informed consent for the publication of the case.

Our patient is a 53-year-old male who presented in 2003 with contact dermatitis after the use of lidocaine and disinfection with chlorhexidine. In 2006, an extensive skin testing by patch, prick, intradermal sampling, and graded challenge was performed as followed. The patch tests were performed with the thin layer rapid use epicutaneous test, using the caine mix (benzocaine, tetracaine, and cinchocaine), the paraben mix (methyl, ethyl, propyl, butyl, and benzylparaben), and the Balsam of Peru. The caine and paraben mix were positive, and the patch test was possibly positive for Balsam of Peru. The prick test performed with preservative-free lidocaine 20 mg/mL (Lidocaïne HCl "Bichsel" 2%, Grosse Apotheke Dr. G. Bichsel, Switzerland) was negative. The intradermal test, performed with lidocaine 20 mg/mL containing methylparaben (Xylocain 2%, AstraZeneca, Switzerland) with 1/10 and 1/100 dilutions, was negative. The subcutaneous challenge test was performed with 10 mg of preservative-free lidocaine 20 mg/mL (Lidocaïne HCl "Bichsel" 2%, Grosse Apotheke Dr. G. Bichsel) and lidocaine 20 mg/mL containing methylparaben (Lidocaïne Streuli 2%, Streuli, Switzerland), both of which were positive and had the appearance of papular eczema within 48 hours.

In 2014, because of the need of an LA for a dermal procedure, the patient underwent allergic testing to 3 other LAs that had not been previously tested. The investigations exclusively included drug provocation tests. The subcutaneous challenge tests were performed with mepivacaine 20 mg/mL (Mepivacain Sintetica 2%, Sintetica, Switzerland), bupivacaine 5 mg/mL (Bupivacain Sintetica 0.5%, Sintetica, Switzerland), articaine 40 mg/mL with epinephrine (Ultracain D-S Sanofi-Aventis, Switzerland), and articaine 10 mg/mL without epinephrine (Ultracain 1%, Sanofi-Aventis, Germany). The test was positive after 48 hours with mepivacaine, and after 60 hours with bupivacaine, in the form of a diffused erythema (Figure 2). The test was negative with both articaine solutions.

The patient also had a history of erythroderma to cotrimoxazole approximately 35 years ago. Since then, sulfonamide antibiotics have not been used in this patient. The patient never presented angioedema, asthma, hypotension, or any other systemic symptom.

DISCUSSION

The results of allergic testing performed in 2006 and 2014 showed that the patient suffered from a delayed-type hypersensitivity to a caine mix, parabens, and amide LAs (lidocaine, bupivacaine, and mepivacaine) but not to articaine. Ester LAs undergo hydrolysis by plasmatic esterases, resulting in the formation of PABA metabolites, which are highly antigenic and are thought to be the cause of true allergies to ester LAs.[3] To be immunogenic, xenobiotics must be large in molecular weight and possess multiple valences to be recognized by immune cells. Most drug molecules are too small and must combine with other molecules that act as carriers to induce an allergic reaction. In the case of sulfonamide antibiotics and some ester LAs, the common phenyl ring containing an amine substitution initiates the formation of an immunogenic complex.[6] Ester LAs and parabens commonly cross-react.[5] A previous study demonstrated that the

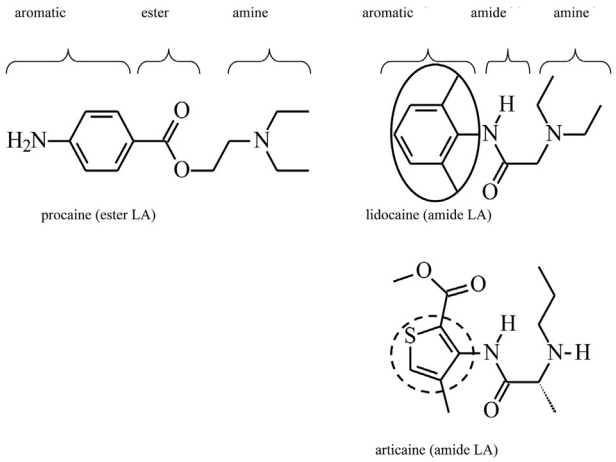

FIGURE 1. Chemical structures of procaine, lidocaine, and articaine. The meta-xylene (*solid line*) and the thiopene (*dashed line*) are highlighted.

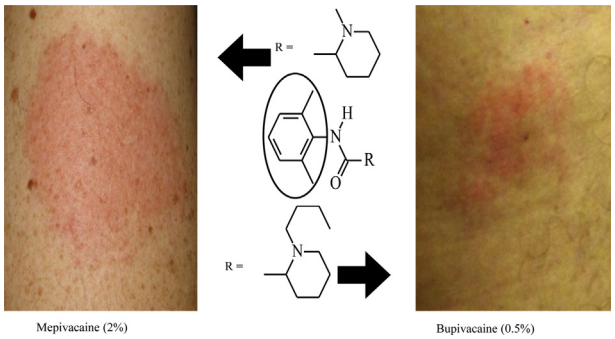

FIGURE 2. Diffused erythema observed 48-60 hours after subcutaneous injection of mepivacaine (*left*) and bupivacaine (*right*). The meta-xylene ring is highlighted.

rate of cross-reactions to parabens in para-phenylenediamine- and benzocaine-positive patients combined was 2%.[7] Although no specific testing to ester LAs was performed in our patient, the patch test for the caine mix was positive. Therefore, it would be reasonable to avoid the use of ester LAs in this patient.

Amide LAs are biotransformed in the liver.[6] Allergic reactions to amide LAs are less frequent due to the lack of PABA formation, but cross-reactivity among amide LAs has been reported.[8] Articaine is classified as an amide LA.[6] However, articaine differs from the other amide LAs because it contains a thiophene ring (Figure 1). In addition, articaine contains an ester group so that hydrolysis into its inactive metabolite articainic acid occurs in the plasma by nonspecific cholinesterases. Articainic acid is partly metabolized by the kidney into articainic acid glucuronide.[9] Articaine has been suggested as being less allergenic than other LAs.[5] This has been illustrated by Bircher et al,[10] who reported a case of delayed hypersensitivity to several amide LAs but not to articaine. However, cases of allergies to articaine have been reported in the literature.[11] Interestingly, our patient presented delayed-type hypersensitivity reactions to LAs containing a meta-xylene component, whereas no reaction to articaine, which is a thiophene derivative, was observed. To the best of our knowledge, the antigenic component responsible for the allergy to amide LA has not been identified. Therefore, we propose that the meta-xylene chemical entity could be the common antigenic determinant in rare cases of hypersensitivity to both ester and amide LAs. The management of such cases is difficult. For our patient, we proposed the use of articaine 1% or 2% for minor intervention to be used according to the manufacturer's instructions. This product is available in Germany, whereas in our country (Switzerland), it is only available for anesthesia in clinical dentistry. For major interventions, general anesthesia should be considered as the best option in this specific case. Our patient has never presented hypersensitivity to the following drugs, which do not contain a meta-xylene component: nonsteroidal anti-inflammatory drugs, codeine, amoxicillin, cephalosporin, and midazolam. The patient was counseled that any of these drugs could be used if needed. We also provided a list of essential drugs not containing meta-xylene that can be used by the patient in case of emergency, for example, fluoroquinolone and macrolide antibiotics, clopidogrel, atropine, digoxin, furosemide, nitroglycerine, clonazepam, clemastine, suxamethonium, and labetalol. To the best of our knowledge, less than 20 commercially available drugs contain a meta-xylene component: for example, rilpivirine (antiretroviral drug), lidamidine (antidiarrheal agent), isonixin (nonsteroidal anti-inflammatory drug), xipamide (diuretic), ranolazine (treatment of coronary heart disease), tocainide, and pilsicainide (antiarrhythmic agents). Except for rilpivirine, all these drugs are not commonly used, and are therefore easily avoidable.

In 2014, additional testing was performed with mepivacaine, bupivacaine, and articaine, due to the need of an LA for a dermal procedure. The investigations were exclusively drug provocation tests. Because of the patient medical history, the risk of systemic symptoms was probably moderate. Skin testing was not performed because the final aim was to identify an LA that could be safely used in our patient. In the case of negative skin prick and intradermal tests, subcutaneous provocation tests may be necessary to complete the procedure,[12] and the provocation test is widely considered to be the gold standard to establish or exclude the diagnosis of hypersensitivity to a given substance.[13] The investigations performed in 2006 in our patient showed that the prick test and the intradermal test with lidocaine were negative, whereas the subcutaneous challenge was positive. According to Fuzier et al,[12] choosing the appropriate tests and the order of their use remains controversial. In their retrospective series, some centers used prick tests first, whereas others used more first intradermal reaction tests or subcutaneous challenges.

In conclusion, we presented a rare case of delayed hypersensitivity reaction to amide LAs, parabens, and probably ester LAs. All drugs causing hypersensitivity in our patient contained a meta-xylene entity, which suggests that meta-xylene could be the eliciting epitope in amide LAs allergies. In such cases, articaine, which is a thiophene derivative, could be an alternative when an LA is needed.

Acknowledgments

The authors would like to thank the patient for allowing publication of this case.

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts.

Received for publication June 9, 2015; revised July 28, 2015; accepted for publication August 3, 2015.

Available online October 1, 2015.

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2213-2198

http://dx.doi.org/10.1016/j.jaip.2015.08.005

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