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The needle in the haystack: allergic anaphylaxis caused by the local anesthetic articaine

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Local anesthetics (LA) are extensively used drugs with an excellent benefit-risk profile. The vast majority of immediate-type adverse reactions can be attributed to non-immune mediated pharmacological effects of LA or psycho-vegetative reactions. Clinical symptoms of these reactions often closely resemble anaphylaxis, including hypotension, tachycardia and subjective feelings such as general weakness, heat or vertigo. However, true IgE-mediated allergic anaphylaxis due to LA is so exceedingly rare, that the question arises whether it does occur at all. Consequently, neither commercial skin test reagents nor validated IgE-measurements are available (1).

A 28-year-old man requiring dental procedures was referred to our allergy clinic with suspected LA-associated anaphylaxis for further evaluation. In March 2011 the patient underwent a dental anesthesia by local injection of the LA Septanest™, containing articaine, epinephrine, as well as the preservatives sodium meta-bisulfite and methyl-4-hydroxybenzoate. Only a few minutes after injection and before starting dental treatment, he suffered a feeling of heat and subsequently developed generalized wheals. The patient experienced dizziness due to measurable cardiovascular depression and nausea. After emergency treatment including fluid replacement, corticosteroids (betamethasone) and antihistamines (clemastine) the symptoms quickly resolved. In the context of this anaphylaxis episode no other potential elicitors such as drugs, foods or concomitant infectious diseases could be evaluated.

Allergologic workup was performed 3 months later. Initially, IgE-mediated natural latex allergy was excluded by an inconspicuous history, negative latex-specific IgE and negative skin testing. Thereafter, skin prick testing with a series of different undiluted LA including articaine, articaine combined with epinephrine, mepivacaine, procaine, prilocaine and prilocaine combined with epinephrine, revealed unequivocally positive immediate wheal-and-flare responses to both articaine preparations. Intradermal testing with serial dilutions of articaine showed positive immediate reactions even down to the highest dilution. A wheal diameter ≥ 5mm was considered as a positive reaction, according to international guidelines. Positive responses, even in case of diminished erythema by the vasoconstrictor epinephrine, could be clearly distinguished from the wheal caused by the intradermal injection itself (**table 1**). Therefore, an IgE-mediated hypersensitivity to articaine was strongly suggested. A basophil activation test (BAT) with articaine failed to reveal any positive results. Following negative skin testing

Table 1 *- Results of intradermal testing (–, negative test result)*

Active substances	Dose [mg/mL]	Wheal diameter
Articaine	1	14 mm
	0.1	11 mm
	0.01	11 mm
	0.001	9 mm
Articaine (multi-dose preparation)	4	14 mm
(Epinephrine	0.0006)	
(Sodium meta-bisulfite	0.0025)	
(Methyl-4-hydroxybenzoate	0.005)	
Articaine (multi-dose preparation)	0.4	9 mm
	0.04	9 mm
	0.004	8 mm
Mepivacaine	1	7 mm
	0.1	–
	0.01	–
	0.001	–
Procaine	1	–
Prilocaine	2	–
Prilocaine (multi-dose preparation)	1	–
(Epinephrine	0.00091)	
(Sodium meta-bisulfite	0.001)	
(Methyl-4-hydroxybenzoate	0.002)	

results, controlled challenge testing was done with the alternative LA procaine, prilocaine combined with epinephrine, and mepivacaine. These LA were injected subcutaneously into the extensor side of the upper arms in incremental doses, starting with 0.1 mL of the undiluted LA followed by 0.2, 0.5, 1.0 and 2.0 mL. These LA were all well tolerated without any side effects up to the cumulative dosage of 3.8 mL.

Throughout the world, about 6 million patients every day receive LA injections. Adverse reactions, occurring in 0.1 to 1% of applications, are rare and may be attributed to different pathomechanisms (2,3). A delayed and localized oedematous swelling could represent a type IV allergy or an episode of hereditary angioedema, triggered by intraoral manipulations. Toxic effects of LA on the central nervous or the cardiovascular system can occur after a high dosage, large-area mucosal application or after accidental intra- or paravasal injection (2,3). Pharmacological side effects associated with epinephrine, a vasovagal reflex or a psychosomatic panic reaction should be also taken into account (4). The symptoms of these "pseudo-allergic" reactions may closely imitate IgE-mediated anaphylaxis (3). Moreover, preservatives in LA preparations have to be considered as causative agents for anaphylaxis.

Even if immediate-type allergic reactions to LA are extremely rare, the potential of IgE-mediated allergy against this class of drugs still exists, as shown by case reports. Venemalm et al. were able to demonstrate mepivacaine-specific IgE-antibodies (5). Calderon et al. described anaphylaxis after regional anesthesia with levobupivacaine and ropivacaine (6). Immediate-type LA allergy was diagnosed based on the timing of serum histamine and tryptase levels as well as positive skin prick test results (6).

In our patient several facts and results strongly suggested an IgE-mediated allergy against articaine. First, clinical symptoms of anaphylaxis, such as generalized wheals, cardiovascular and gastrointestinal symptoms appearing within a few minutes after injection were convincing. Second, we ascertained positive intradermal test results with articaine in dilutions from 1:10 down to 1:10.000 in view of a huge number of negative test results in 220 control patients tested within the last 6 years in our allergy clinic. The 1:10 dilution of articaine produced false positive immediate reactions in a rather small number of patients (in 10 out of the 220 mentioned). But in these 10 patients, further dilutions proved to be clearly negative. Third, allergy was substance-specific as demonstrated by the tolerated LA procaine, prilocaine and mepivacaine. The structural differ-

ences between articaine, which is a thiophene derivative (with presence of a thiophene ring and an additional ester group), and the amino-acylamides prilocaine and mepivacaine, containing a methylated phenyl ring, reasonably explain this apparent lack of cross-reactivity (7,8). Fourth, by skin and challenge testing a series of LA containing the preservatives sodium meta-bisulfite and methyl-4-hydroxybenzoate, a causative role of these agents could be excluded. BAT was proposed as a complementary method for *in-vitro* diagnosis of drug allergy. But until now, the sensitivity of BAT for confirming drug hypersensitivity is generally low.

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