



Allergy to local anesthetics: Reality or myth?

Jean-Marc Malinovsky¹, Anca M. Chiriac², Charles Tacquard³, Paul Michel Mertes³, Pascal Demoly²

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1. CHU de Reims, pôle URAD, hôpital Maison-Blanche, service d'anesthésie-réanimation, 51092 Reims, France
2. CHU de Montpellier, hôpital Arnaud-de-Villeneuve, division allergie, département de pneumologie, 34295 Montpellier, France
3. Hôpitaux universitaires de Strasbourg, département d'anesthésie-réanimation, 67091 Strasbourg, France

Correspondence:

Jean-Marc Malinovsky, CHU de Reims, pôle URAD, hôpital Maison-Blanche, service d'anesthésie-réanimation, 51092 Reims, France.
jmmalinovsky@chu-reims.fr

■ Key points

The incidence of allergic reactions to local anesthetics is low.
Most cases involve a psychogenic reaction rather than an allergic reaction.
Additives and preservatives added to local anesthetics may cause allergic reactions.
Vascular resorption of epinephrine-containing local anesthetics may produce cardiovascular signs similar to an allergic reaction.
Diagnosis of allergy to local anesthetics must be established by skin testing and provocative challenge.

■ Points essentiels

L'incidence des allergies aux anesthésiques locaux est très faible, < 0,1 % des réactions adverses déclarées. Le plus souvent les réactions sont des réponses psychomotrices à l'injection, ou des réactions allergiques imputables aux adjuvants des solutions d'anesthésiques locaux ou un effet systémique de l'adrénaline des solutions adrénalinées. Pour affirmer le diagnostic d'allergie aux anesthésiques locaux un bilan allergologique est nécessaire avec la réalisation de tests cutanés ainsi que le test de réintroduction. Compte tenu du nombre important d'anesthésies réalisées tous les jours et le très faible nombre de cas enregistrés de véritables allergies, les anesthésiques locaux sont des médicaments sûrs pour les patients allergiques.

The Inca chewed coca leaves for their local anesthetic effects in addition to stimulant properties such as auditory and visual hallucinations. Koller was the first to introduce cocaine as a local anesthetic for eye surgery [1]. The modern local anesthetics are structurally related to cocaine, but have no potential of addiction

and produce less arterial hypertension or vasoconstriction than cocaine. The molecular structure of local anesthetics consists of a lipophilic aromatic ring connected to a hydrophilic amine group by an intermediate bond that determines the classification of the different agents as ester, amide, ketone or ether local

TABLE I
Local anesthetics in clinical use

Amide group	Ester group
Lidocaine	Procaine
Prilocaine	Chloroprocaine
Mepivacaine	Tetracaine
Bupivacaine	
Ropivacaine	
Articaine	

TABLE II
Differential diagnosis of allergy to local anesthetics

Psychogenic responses

- Vasovagal syncope
- Panic attack
- Spasmophilia crisis with hyperventilation

Adverse reactions unrelated to local anesthetics

- Additives or preservatives
- Epinephrine added to local anesthetic solution
- Latex
- Antibiotics

anesthetics. The local anesthetics used in clinical practice belong to the amide or the ester groups (table I). Local anesthetic agents block nerve conduction and are used for local or regional anesthesia.

Adverse effects of local anesthetics

The most serious adverse effect of local anesthetics is their systemic toxicity which affects the central nervous system and cardiovascular system. This can occur after massive resorption from a large dose of local anesthetic or after inadvertent intravascular injection. The free fraction of local anesthetic is responsible for the systemic toxicity. Classically, the first signs are subjective neurological signs (paresthesias, auditory and visual hallucinations), followed by severe neurological complications such as seizures or coma. These signs are precursors of cardiac signs (except in cases of intravascular injection) with atrioventricular conduction delay followed by ventricular dysrhythmia or cardiac arrest.

In addition to their systemic toxicity, large doses of lidocaine and prilocaine can cause methemoglobinemia in children.

Hypersensitivity reactions to local anesthetics

Allergic reactions have also been reported. Monk reported the case of a dentist who developed contact dermatitis after chronic application of apothésin, an ester local anesthetic [2]. Several

other cases of contact dermatitis were subsequently published, but few patients developed anaphylaxis [3]. The causative local anesthetics were from the ester group, and the culprits were found to be para-aminobenzoic acid, a metabolite of ester hydrolysis, or additives such as parabens [4,5]. After introduction of the amide local anesthetics in the 1940s, the number of cases of allergy to local anesthetics decreased.

Allergic reactions to local anesthetics are uncommon, mainly described after dental or facial surgery. Most adverse effects are not related to the local anesthetic itself [6] (table II). For instance, neurological symptoms such as vasovagal syncope (pallor, bradycardia), panic attack or spasmophilia crisis (lipothymia, sensation of heat, paresthesia, rash, polypnea, hyperventilation and chest tightness) are frequently reported. Epinephrine added to decrease the rate of resorption of local anesthetic solutions (or direct intravenous passage during anesthesia for dental surgery) might cause tachycardia and cardiac arrhythmias in some patients. Contact with latex gloves can also induce anaphylaxis to latex, and the antibiotics given for prophylaxis of postoperative infection can also cause hypersensitivity reactions.

Local anesthetics are weakly antigenic due to their low molecular weight (< 300 daltons). Amongst allergic reactions to local anesthetics, delayed cutaneous reactions such as eczema are the most frequent. This corresponds to a type IV immune reaction in the Gell and Coombs classification. It is possible to derive specific T cell clones from these patients [7]. Immediate allergic hypersensitivity reactions (type I reactions) are rare. Clinical manifestations range from low-grade cutaneous, neurological, cardiovascular or respiratory signs to severe reactions including life-threatening anaphylactic shock. Specific IgE-mediated allergy to local anesthetics has never been demonstrated [8].

How to investigate patients with suspected allergic reactions

Many patients claim to be allergic to local anesthetics. In view of the many differential diagnoses, allergy screening is mandatory to confirm the diagnosis of allergy. Administering general anesthesia to such patients to avoid the allergy workup would be a mistake, with potential legal consequences in case of a serious adverse event. An increase in blood concentrations of histamine and tryptase is helpful to support the diagnosis. Two measurements are recommended: one rapidly after treating the anaphylactic episode (around 30–60 minutes afterwards) and later for baseline values. Skin testing with prick tests then intradermal injection with incremental concentrations of local anesthetics (from 10^{-3} to 10^{-1} solution of a 1–2% anesthetic vial free of epinephrine) can be performed. The criteria for a positive skin test are the same as for all drugs [10]. Skin tests can also be used to investigate cross-reactivity, which is common with the esters, but not with the amides or between the esters and amides.

Skin tests are rarely positive (table III). In pooled data of a large series of skin tests in patients with a history of adverse reactions

TABLE III

Large series of skin tests and challenge tests in patients referred to allergist consultation for a history of adverse reactions to local anesthetics, adapted from Bhole [11]

Authors	n	History	Prick tests	IDR tests	Challenge tests	Comments
Incauto et al., 1978 [12]	71	History of adverse reaction to LA	3/59	5/59	0/50	Challenge with no reaction, despite positive SPT
deShazo et al., 1979 [13]	90	Screening after immediate hypersensitivity reactions	0/90	10/90	0/90	Challenge with no reaction, despite positive SPT
Fisher and Graham, 1979 [14]	27	History of adverse reaction to LA	–	1/27	0/26	No reaction
Chandler et al., 1987 [15]	59	History of adverse reaction to LA	0/59	–	0/54	No reaction
Wasserfallen and Frei, 1995 [16]	28	History of adverse reaction to LA	4/28	10/28	0/28	No reaction
Gall et al., 1996 [8]		History of adverse reaction to LA	0/177	0/177	3/177	One delayed reaction, 2 immediate reactions
Fisher and Bowey, 1998 [17]	208	History of adverse reaction to LA	–	4/202		4 patients with IHR, 4 with DHR and 39 possible reactions to additive
Wildsmith et al., 1998 [18]	25	History of adverse reaction to LA	–	–	1/25	One true allergy to LA
Triose et al., 1998 [19]	386	History of adverse reaction to LA (without preservative)	13/386	3/386	0/13	No reaction in patients with positive IDR
Hein et al., 1999 [20]	32	Evaluation of systemic provocative tests vs placebo	0/32	–	1/32	One positive challenge with placebo
Cetinkaya, 2001 [21]	157	157 patients with asthma and atopy, 3/125 with previous history of adverse reaction to LA	0/157	0/157		No reaction in children with atopy or asthma
Nettis et al., 2001 [22]	105 (432)	Challenge test in 432 patients, 105 had a previous history of adverse reaction to LA	0/105	0/105	0/105	No reaction
Astarita et al., 2001 [23]	198	198 challenge tests, 72 with a previous history of adverse reaction to LA	0/198	0/198	0/198	No immediate reaction, 2 delayed reactions, > 1000 uneventful LA new injections
Macy et al., 2001 [24]	252	History of adverse reaction to lidocaine with paraben	3/252	1/252	0/252	3 reactions with paraben, none with lidocaine
Baluga et al., 2002 [25]	25	History of adverse reaction to LA in dental surgery	0/25	0/25	0/25	No allergic reaction 22/25 psychogenic or vasovagal reactions 2/25 delayed reactions
Berkun et al., 2002 [26]	236	History of adverse reaction to LA	0/236	0/236	0/236	1 true reaction
Amsler et al., 2004 [27]	199	History of adverse reaction to lidocaine	–	–	1/199	No allergy 9 vasovagal and 1 psychogenic reaction
Jacobsen et al., 2005 [28]	48	History of adverse reactions to LA	3/48	3/48	2/48	2 allergic immediate reactions 1 allergic delayed reaction
Wohrl et al., 2006 [29]	36	History of adverse reactions to LA	2/36	2/36	2/36	2 positive challenge tests with positive IDR
Fuzier et al., 2009 [30]	286	Retrospective analysis of databases (1985–2006)	1/286	1/286	3/286	3 true allergic immediate reactions 8 other patients in GERAP database over 20 years
Harboe et al., 2010 [31]	135	History of adverse reactions to LA (1995–2006)	0/135	0/135	1/135	1 allergic delayed allergy, 8 patients with allergy to agents other than LA
McClimmon et al., 2011 [32]	178	History of adverse reactions to LA (1992–2008)	1/178	4/178	3/173	
Tomoyasu et al., 2011 [33]	20	History of adverse reactions to LA (2004–2009)	–	3/17	0/13	

to local anesthetics, skin tests were positive in < 0.01%. When challenge tests (re-injection of local anesthetic) were performed, only 17 patients out of 2202 were positive (0.007%). Moreover, in some patients, skin tests may be positive when only placebo is tested, especially when using the plain concentration [8]. This highlights the difficulty of using skin tests alone to confirm the diagnosis.

Some authors have proposed the use of an in vitro leukocyte migration test [9]. However, this test has a high rate of false positives and false negatives.

Provocative challenge in a patient with a previous history of adverse events after injection of local anesthetics is the best way to establish the diagnosis. This is performed by injection of incremental doses of local anesthetic with the patient monitored for 30 minutes to one hour after each administration and up to two hours after the last injection.

Obstetrical analgesia is a common circumstance to investigate patients with a history of adverse reaction to local anesthetics. Skin testing can be performed as in other patients at an allergist consultation. For the challenge test, the Société française d'anesthésie et réanimation (SFAR) and Société française

d'allergologie (SFA) recommend that it should be done on the day of labor, in the obstetrical theater [10]. The anesthetist administers local anesthesia before insertion of the epidural catheter, using the local anesthetic solution that will be used for epidural analgesia of labor, and the obstetrician should be ready to deliver the parturient in case of a reaction to the local anesthesia.

In conclusion, allergy to local anesthetics is rare. In most cases, the signs reported by patients are related to psychomotor responses to trauma or anesthetic technique, or to epinephrine added to local anesthetics. An allergic investigation is mandatory to support or more often to rule out the diagnosis of allergy to local anesthetics, from the skin tests to the challenge test. Considering the number of anesthetics performed every day and the very low number of recorded cases of allergy, other diagnoses must be considered in front of a patient with alleged allergy to local anesthetics. Local anesthetics are safe medicines for allergic patients.

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