

Long-term evaluation of usefulness of skin and incremental challenge tests in patients with history of adverse reaction to local anesthetics

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A variety of adverse reactions to local anesthetics has been described, some of which are thought to be allergic. Different protocols of prick and intradermal skin tests as well as subcutaneous challenge tests are used to select a local anesthetic which can safely be used. Their long-term effectiveness has not yet been assessed. Twenty-eight patients with a history of adverse reaction to local anesthetics were evaluated over a 3-year period. Loss of consciousness occurred in eight patients, skin reaction in nine, and vagal symptoms in eight. Various reactions were recorded in the remaining three patients. Rapid spontaneous recovery was the rule, suggesting that immediate allergic reaction and, in particular, anaphylactic reaction were unlikely. Investigation allowed the selection of a tolerated anesthetic in all cases. Reexposure occurred in 19 patients 16-50 months after evaluation and 6.8 ± 5.5 years after the first reaction. No patient presented a second reaction. In conclusion, adverse reactions to local anesthetics seem to be, in most cases, not allergic in nature. Evaluation protocols are effective in selecting an agent susceptible to tolerance, but are time consuming. However, they probably contribute to an important reassurance effect that is likely to increase tolerance to subsequent local anesthetic administration. Simplification of the protocols and better patient selection are proposed.

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Local anesthetics (LA) are widely used in almost every field of medicine. A variety of adverse reactions has been described. Clinical manifestations include cutaneous, respiratory, cardiovascular, and neurologic symptoms and signs of various degrees of severity. History alone does not allow a precise classification of these reactions. The majority are thought to be toxic or related to the dental or surgical procedure requiring local anesthesia (3). Various types of allergic reactions have been reported, the majority of which are thought to be anaphylactoid. They represent less than 1% of all recorded reactions (5). Different protocols of investigations have been proposed, including skin tests and subcutaneous challenge tests (1, 2, 4, 6), in order to select an LA which can safely be used. Their interpretation may be difficult because a positive skin reaction does not always imply that the patient is allergic to the tested compound (4, 6). Matters are further complicated by

the fact that LA preparations often contain preservative agents such as bisulfite or paraben, to which patients may be hypersensitive (6, 7). Paraben is also structurally homologous with the ester class of LA.

Such protocols are designed to allow the identification of a tolerated LA that can be recommended for subsequent use. There are, however, no data on the long-term effectiveness of these protocols. This study describes our 3-year experience of LA tolerance evaluation and analyzes the late outcome of our patients.

Material and methods

Patients

Between 1 July 1987 and 30 June 1990, 28 patients were referred because they had experienced an adverse reaction to LA (three patients in 1987, seven in 1988, nine in 1989, and nine in 1990). Nineteen

patients were women (68%) and nine were men. The mean age at the time of evaluation was 41.0 ± 13.4 years (range 14–70).

Protocol

According to the protocol used in our hospital, skin tests were performed with solutions of four different anesthetics, used without addition of vasoconstrictor or preservative agents (lidocaine 2%, bupivacaine 0.25%, mepivacaine 0.5%, and procaine 1%). The first step involved prick tests carried out with undiluted solution, followed after 15 min by intradermal tests performed first with a 1/10 diluted solution, and then 15 min later with the undiluted solution. If one of these steps yielded a positive reaction, the substance was not tested further. Positive reaction was defined as a wheal and/or flare of 3 mm in diameter or more. The positive control was a prick test with a solution of histamine dihydrochloride (0.1%), and the negative control saline (0.9%). This preliminary screening allowed the selection of one LA that was subsequently administered in an open way as a subcutaneous challenge test (SCCT) carried out with increasing doses of undiluted solution, injected in the lateral side of the arm, with blood pressure and symptoms being recorded both before and during the 15-min period following the injection. If a first dose of 0.1 ml was well tolerated, three subsequent doses of 0.5, 1, and 2 ml were administered every 15 min. An infusion line was set up before the beginning of the SCCT and maintained for 30 min after the last injection.

Long-term usefulness

In order to assess the long-term usefulness of this evaluation procedure, a questionnaire was sent in July 1990 to each patient, his dentist, and his physician, requesting data on possible LA injections given after the evaluation procedure (date, kind of intervention, duration, type of LA used, signs and symptoms presented, and treatment given in case of adverse reaction). In March 1992, a telephone inquiry to all patients allowed us to update the results.

Results

Initial reaction

Among the 28 patients referred because of adverse reaction to LA, the mean age when reaction occurred was 34.5 ± 14.3 years, with a range of 10–68 years. The interval between reaction and evaluation was 5.7 ± 5.2 years, with a range of 0–20 years. Seven out of the 28 patients (25%) did not remember the date of the reaction, despite its systemic character.

Clinical manifestations were of various types. The

diagnosis of possible anaphylactic reaction was considered in eight patients (29%) in whom sudden loss of consciousness had occurred. Cutaneous reactions (urticaria and angioedema) were recorded in nine patients (32%), of which three were delayed reactions. Strictly vagal symptoms (sweating, lightheadedness, near fainting) had occurred in eight patients (29%), and other types of reactions ascribed to LA intolerance (delayed loss of vision, salivary gland swelling, and delayed local swelling, respectively) in the remaining three patients.

The LA used was lidocaine in 11 patients (five with vasoconstrictors and preservative agents), an unknown LA in 11 others, and articaine with vasoconstrictors and conservative agents in five. In the last patient, the reaction occurred after the administration of oxytocin given during a cesarean section performed under spinal anesthesia with xylocaine and bupivacaine injections.

In 19 out of 28 reactions, LA had been administered for dental and in nine for surgical or obstetric procedures. In three of the latter patients, the reaction occurred after intra-articular injection of a corticosteroid associated with lidocaine and was cutaneous in two and possibly anaphylactic in the third patient. Possible reaction to oxytocin in one patient has already been mentioned. Finally, the concomitant use of a nonsteroidal anti-inflammatory drug was involved in one patient, the subsequent cutaneous reaction being possibly ascribed to this compound rather than to LA.

The most striking feature was that 23 out of 28 patients did not receive any treatment at the time of the reaction and spontaneously recovered without sequelae. Only three of them were given epinephrine and had to be hospitalized: the 30-year-old woman who reacted to oxytocin during cesarean section, a 46-year-old man who reacted to an intra-articular injection of a corticosteroid associated with LA, and a 30-year-old man who reacted during a dental procedure involving injection of articaine and epinephrine. One further patient was treated with diazepam for an epileptic attack following an injection of lidocaine and epinephrine in the course of a skin biopsy, and another patient was treated with ethylefrine following recovery from a syncope which occurred during a dermatologic intervention involving lidocaine injection.

Evaluation procedure

Skin tests. The results of skin tests are displayed in Table 1. Prick tests were positive in 4/28 patients, mostly to lidocaine and bupivacaine. Positive intradermal reaction to a 1:10 dilution was observed in 10/28 patients, mostly to procaine and lidocaine. Positive intradermal reaction to undiluted solution

Table 1. Evaluation of tolerance to LA: results of skin tests (ST)

	Number of positive tests to				No. of reactive patients
	Lidocaine	Bupivacaine	Mepivacaine	Procaine	
PT	3/28	2/28	1/28	1/28	4/28*
ID 1/10	4/28	3/28	2/28	5/28	10/28
ID 1/1	11/22	16/22	1/23	22/22	22/23

PT=prick tests.

ID=intradermal tests.

* One patient reacted to all prick tests and to negative control.

was found in 22/23 patients (96%), mostly to procaine (22/22 = 100%), bupivacaine (16/22 = 73%), or lidocaine (11/22 = 50%).

Subcutaneous challenge test (SCCT). Fourteen patients were challenged with lidocaine, 11 with mepivacaine, three with bupivacaine, and one with procaine (one patient was challenged with two LA). In 25 of 29 SCCT, no sign or symptom occurred. During the remaining four SCCT, local swelling at the site of injections occurred twice (once with lidocaine and once with bupivacaine), whereas tinnitus and dizziness were recorded in one test each. No modification of blood pressure nor any other sign of intolerance was noticed in these cases (Table 2).

Long-term outcome

Nineteen patients (68%) were reexposed to LA during the 29 ± 11 months (range 16–50 months) of follow-up after the initial evaluation. The interval between the initial reaction and the subsequent LA was 6.8 ± 5.5 years (range 0–20). Thirteen out of 19 patients were reexposed to LA within the first year following the tolerance evaluation, and seven of these 13 within 2 months. A dental procedure was involved in 15 of the 19 patients (79%). Multiple exposures were given to 13/19 patients (more than 10 injections in two, at least six injections in one, three and two injections each in five patients). A maxi-

Table 2. Evaluation of tolerance to LA: results of subcutaneous challenge tests (SCCT)

	Lidocaine	Bupivacaine	Mepivacaine	Procaine	Total
No. of patients	14	3	11	1	29*
Symptoms					
Cutaneous	1	1	—	—	2
Tinnitus	1	—	—	—	1
Dizziness	1	—	—	—	1
No symptom	11	2	11	1	25

* One patient was challenged with two LA.

Table 3. Local anesthetics used during subsequent exposure

Anesthetics used	No. of patients		
	Recommendation made after evaluation	Reexposure with recommended preparation	Combined preparation
Lidocaine	10	10	3
Bupivacaine	1	2*	
Mepivacaine	7	7	
Procaine	0	0	
Articaine	1	2*	2
Total	19	21*	5

* Two patients were reexposed to two different LA.

um of 20 injections was given in one patient. Recommendations derived from the tolerance evaluation were followed in the majority of cases, as shown in Table 3. However, five patients were reexposed to preparations containing vasoconstrictors and preservative agents (three to lidocaine and two to articaine).

One of the 19 reexposed patients complained of nausea and another of dizziness, symptoms which appeared immediately after the injection, were similar to the initial reaction, and did not require any treatment. One of these two patients had been exposed to a combined preparation. Two other patients reported that subsequent anesthetics were of too short a duration, probably because associated epinephrine was not used for fear of intolerance to the preservative agent included in these preparations (sulfite). One patient was never reexposed to LA because he did not find a dentist ready to treat him, and another one preferred to suffer rather than risk another systemic reaction. Reexposure was well tolerated in the remaining 13 patients.

Discussion

This study confirms that assessment of patients with history of adverse reaction to LA is difficult: the history of the reaction is often remote or imprecise; the implicated drug is often unknown; the symptoms and signs are various, sometimes systemic or only cutaneous; and, most surprisingly, the vast majority of these reactions are transient and do not require any treatment. The psychological consequences, however, are important and may warrant a tolerance evaluation.

Precise classification of the manifestation is therefore controversial. Vagal reactions are clearly involved, as are skin reactions. Sudden loss of consciousness can be of vagal, toxic, or anaphylactic origin. Its transient nature and the rapid and spontaneous recovery without sequelae, as well as the absence of any other sign of allergic involvement in

other organs, make us consider that true anaphylaxis did not occur in our patients and is probably extremely rare. Different studies have also emphasized that opinion (1, 2, 4-7). Moreover, IgE to LA has never been described in adverse reactions to LA.

In this setting, immunologic methods are of limited value. The frequency of false positive skin tests, especially intradermal, has been estimated to be 10-15% (4, 6) and was 36% in our study. We found an even higher rate when undiluted solution was used (96% of all patients, and 100% of procaine tests; Table 1). Challenging some patients with positive skin test has been proved to be safe, leading to no adverse reaction, as reported by Chandler et al. (2), and suggesting that a positive skin reaction may be of irritative rather than allergic nature. Up to now, our skin tests allowed us to select in all cases a nonreacting LA that could be subsequently administered in a subcutaneous challenge test. This remained the most useful procedure. None of our 30 patients experienced serious adverse reaction to the challenge (Table 2), which in all cases allowed us to recommend an LA for subsequent exposure. It was, of course, not possible for us to forecast for how long such an LA would be safe. We have not observed changes occurring up to 2 years after the challenge. But one must remain cautious since no solid data on the validity duration of a negative challenge are available.

Our results imply that intradermal testing with undiluted solutions should be abandoned in favor of prick tests because false positive results are too frequent. But since occasional patients could present with a positive reaction to all prick tests, we suggest that intradermal testing with 1:10 dilution be reserved for such patients, and, as proposed by Chandler et al. (2), that prick tests with undiluted solutions be followed by subcutaneous challenge tests. This modification of the testing procedure makes it less time consuming.

The results of different studies on the evaluation of patients suspected to react to LA have been published (1, 2, 4-7). However, long-term survey of such patients is lacking. Our study showed that the evaluation of patients was useful and accurate in selecting an LA that was tolerated during subsequent administration. In our series of 28 patients, only two of the 19 patients reexposed to LA after a mean follow-up period of 30 months experienced a tran-

sient minor reaction which was similar to the initial reaction and did not require any treatment. A reassurance effect may have played a role both for the patient and the dentist or physician, as attested by the fact that most subsequent LA administrations happened soon after the evaluation procedure. However, the role of preservative agents (especially bisulfite) is still difficult to assess and has not been addressed in our study. Five of the 19 patients who were reexposed to an LA received a preparation that contained both vasoconstrictors and a preservative agent, without untoward effect (Table 3).

In summary, it seems difficult to establish a need for immunologic tolerance evaluation of patients with history of LA adverse reaction. On one hand, one might argue that a better patient selection based on history and clinical manifestations of LA intolerance could avoid a time-consuming tolerance evaluation. On the other hand, since anxiety predominates and probably influences the occurrence of the noncutaneous signs and symptoms, such a tolerance evaluation might improve the tolerance of subsequent LA administrations. It is therefore useful to offer this possibility to dentists and patients who fear adverse reactions to LA. Shortened protocols, omitting the time-consuming steps of intradermal tests with diluted and then undiluted solutions, should be evaluated prospectively and their usefulness assessed on a long-term basis.

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