

Review Article

Hypersensitivity to local anaesthetics – update and proposal of evaluation algorithm

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Local anaesthetics (LA) are widely used drugs. Adverse reactions are rare but may be caused by delayed-type hypersensitivity reactions and probably also immediate-type reactions. As it is not always easy to clinically differ between these subtypes, allergy skin testing should be considered. Although numerous test protocols have been published, how patients with hypersensitivity reactions to LA are ideally evaluated remains a topic of discussion. This review attempts to generate a comprehensive update on allergic reactions to LA and to present an algorithm that can be used for the evaluation of patients suspected with immediate- and delayed-type immune reactions. Literature was examined using PubMed-Medline, EMBASE, Biosis and Science Citation Index. Based on the literature, the proposed algorithm may safely and rapidly distinguish between immediate-type and delayed-type allergic immune reactions.

Key words: allergy; contact allergy; lidocaine; local anaesthetics; treatment; type 1; type 4.
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Local anaesthetics (LAs) have been used for their analgetic effect since the late 19th century (1). Although 6 millions individuals are injected each day around the world (2), adverse reactions remain rare, e.g. in the UK, 70 million cartridges of lidocaine and prilocaine are administered each year for dental procedures but only 249 cases of adverse reactions were reported (3). Hypersensitivity reactions are especially rare and account for less than 1% of all adverse reactions (4–7); no reactions were observed in one prospective study including 5018 consecutive dental patients (8). The causative pathomechanism of an adverse reaction is most often a delayed-type hypersensitivity reaction but there may also be an immediate-type reaction (9,10). However, to our knowledge, specific immunoglobulin E (IgE) to lidocaine has only been indirectly identified in two cases (11, 12).

A patient reacting to an LA may be mislabelled 'allergic' although the reaction experienced was autonomic or toxic in origin. As there will be concern in giving such a patient LAs in future treatments, allergy skin testing should be considered and in recent decades various test protocols

(4, 10, 13–16) have been suggested. In this review, we provide an update and propose an evaluation algorithm for hypersensitivity reactions to LAs.

Materials and Methods

Literature was examined using PubMed-Medline, EMBASE, Biosis and Science Citation Index. Search terms included allergic reaction, adverse reaction, toxicity, drug reaction, LA, anaesthesia, dental anaesthesia, delayed-type hypersensitivity, immediate-type hypersensitivity, anaphylactic, anaphylactoid, type 1 immune reaction, type 4 immune reaction, allergy skin testing, patch testing, prick testing and intradermal testing. Additionally, the databases were searched by the use of the 'related articles' function and by searching the publications by specific authors in the scientific area. Finally, references were localized by the use of reference lists in review articles.

Pharmacology

LAs have three components, a lipophilic (aromatic) group, an intermediate chain linkage and

a hydrophilic (amine) group (Fig. 1). They are classified as ester or amide compounds based on the intermediate chain (Table 1). As a mnemonic, all amides are spelled with two 'i's, e.g. lidocaine. Based on a thiophene ring, amide LAs are further divided into two subgroups, aminoacylamides (e.g. lidocaine, bupivacaine, articaine, mepivacaine and prilocaine) and aminoalkylamides (e.g. procainamide and dibucaine). Esters are metabolized by pseudocholinesterase to p-aminobenzoic acid (PABA) and in case of altered enzyme function, the risk of adverse events is increased (17). Amides are metabolized by hepatic microsomal enzymes. Thus, patients with decreased liver function are more likely to experience adverse events (17).

LAs irreversibly block impulse conduction along nerve axons. The combination of small molecule size and aromatic ring structure allow LAs to rapidly interact with the cells' voltage-gated sodium channels and inhibit their function (18). They are applied either topically (skin and mucosa) or through injection (subcutaneously, as deep infiltration or as instillation around the spinal cord). At the site of administration, LAs provide a complete but temporary analgesia. LAs differ in their potency and duration of action; bupivacaine is 16 times more potent than procaine and has longer duration of action (18). Long dura-

Table 1. Local anaesthetics are chemically either esters or amides. All amides are spelled with two 'i's, e.g. lidocaine. This list is not comprehensive

Esters	Amides
Benzocaine	Articaine
Chloroprocaine	Bupivacaine
Cocaine (methylbenzoylcegonine)	Dibucaine (Cinchocaine)
Procaine (novocaine)	Etidocaine
Proparacaine (alcaine)	Levobupivacaine
Tetracaine (amethocaine)	Lidocaine (Lignocaine)
	Mepivacaine
	Prilocaine
	Ropivacaine
	Sameridine
	Tonicaine

tion of action depends on (i) strong protein binding by large polar groups on the molecules; (ii) the addition of vasoconstrictors to delay tissue drug removal by decreasing blood flow, and (iii) the fact that ester links are easily hydrolysed than amide links (17, 18).

Allergic Reactions

Immune reaction pathomechanisms

Two types of allergic reactions to LAs are recognized: IgE-mediated type 1 reactions and T-cell-mediated type 4 reactions. As prevalent subtypes of ester and amide LAs are available both as topical preparations and injectable agents, both reaction types may be caused by members of both groups (19).

Immediate type 1 reactions are characterized by release of histamine and other mediators from mast cells and basophils, following IgE antibody bridging by the allergen. A rapid increase in vascular permeability as well as contraction of smooth muscles lead to symptoms such as urticaria, angioedema, bronchospasm, cardiovascular depression and in severe cases shock (20, 21). The severity of an anaphylactic reaction depends on allergen dose, entry route, and the amount of allergen-specific IgE antibody (22). If suspected, plasma tryptase (taken approximately 1 hr after the beginning of the reaction) or spot urinary methyl histamine should be measured to assess whether mast cell degranulation has occurred. Immediate type 1 reactions are usually observed within seconds to minutes but may require 1–4 hr to develop (4, 23). Mast cell degranulation may also occur through a non-IgE-mediated mechanism although little is known about its frequency and exact mechanism (e.g. urticaria and angioedema may perhaps be initiated by a delayed-type T-cell-mediated immune reaction) (24).

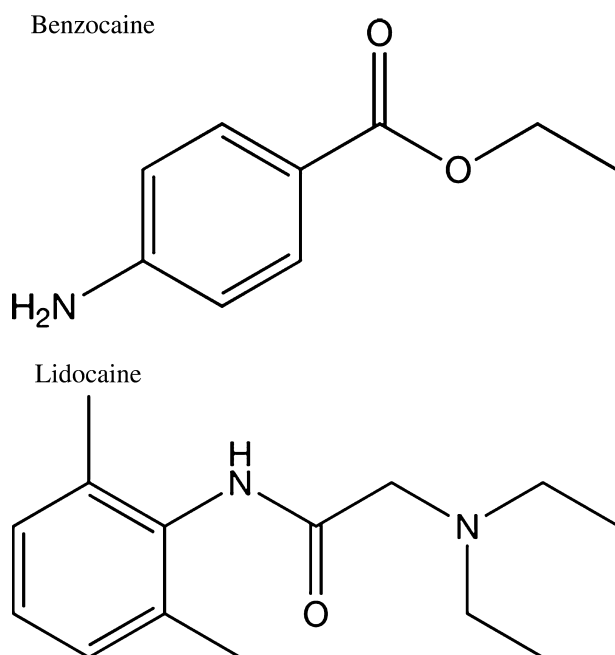


Fig. 1. Local anaesthetics have three different components, a lipophilic (aromatic) group, an intermediate chain linkage and a hydrophilic (amine) group. They are classified as ester or amide compounds based on their intermediate chain. This figure presents one ester (benzocaine) and one amide (lidocaine).

Delayed-type 4 hypersensitivity reactions are most often induced by skin contact with topical preparations but localized oedema may also develop following injection (25–27). It is a dermo-epidermal response where initial exposure of T cells to antigens presented by Langerhans' cells and other dendritic cells lead to sensitization. Upon re-exposure, sensitized memory T cells release chemokines and cytokines that attract and activate effector T cells as well as endothelial cells and keratinocytes (28). Contact dermatitis usually appears within 24–72 hr but may be detected clinically after only 2 hr (28). Type 1 and type 4 reactions may, in a few cases, be hard to separate clinically because no clear temporal separation has been determined (4).

Causative allergens

Allergic type 1 and 4 reactions are most often caused by ester compounds (19, 29). Esters are metabolized to PABA, which is responsible for their strong allergenic potential (15, 19). Furthermore, preservatives in LA preparations may cause both type 1 and 4 allergic reactions (19, 30, 31). The most widely used preservatives are methylparaben and propylparaben and they have breakdown products that are chemically similar in structure to PABA (19). As parabens may cause a burning sensation on injection, paraben-free preparations are now available [leading to a suggested decrease in the number of allergic reactions in the USA (32)]. According to the Danish Medicines Agency, parabens are still widely used in LAs in Denmark. Additional potential allergens are sodium metabisulfite and sodium bisulfite, antioxidants present in epinephrine-containing LAs (33, 34). As many foods, drugs, wines, and beverages are preserved with sulfites, sulfite-containing LAs should be avoided in patients with relevant histories of food allergies (33–36).

Cross-reactivity

Immediate- and delayed-type hypersensitivity reactions are clinically independent (37, 38) and cross-reactivity patterns may not be transferred (39, 40). Cross-reactivities are common within both the ester and amide group (38, 41–48) but cannot be predicted from the structure of the ionisable amide group (26, 41, 49–51). It is generally accepted that cross-reactivity between esters and amides does not occur because their breakdown products differ (52, 53), but one case with immune reactions to both esters and amides has been reported (54). Furthermore, one study showed two patients with positive patch test reactions to

both lidocaine and benzocaine (38). It is unknown whether this was a consequence of co-sensitization or cross-reactivity.

Adverse Reactions and Differential Diagnoses

Toxic reactions

Toxic reactions may be observed if a high dose of LA is used (e.g. at liposuction) or in case of accidental intravascular injection (55). As blood is aspirated in 2–30% of all injections (29, 56), accidental vascular injection of LA may occur. Thus, the risk of toxic reactions may be minimized by staying within safe dosage parameters and using safe injection techniques (57). Cardiovascular toxicity usually occurs at blood concentrations that are higher than those required to produce central nervous system toxicity. Symptoms include convulsions, hypotension, bradycardia and eventually cardiovascular collapse, coma and death (18, 58). Local oedema (without systemic reactions) following injection can be caused by metallic ions such as zinc, copper and nickel (57) or by cellular, vascular or neural damage caused by toxic LA levels (9).

Autonomic reactions

Many patients experience sweating, dizziness, nausea and light tachycardia before minor surgery. Nearly 22% patients visiting a travel health clinic were afraid of injections, and among 8.2%, the fear was unreasonably intense (59). Fainting was experienced by 2% Norwegian high school students during dental injection and by 7% during medical injection (60). Fainting led to future avoidance of necessary treatment in 5–7% students (60). In rare cases, autonomic reactions may be secondary to LA vasoconstrictor effect (61).

Differential diagnoses

C1 esterase inhibitor deficiency may lead to acute angioedema when such patients are exposed to surgical procedures (62, 63). Furthermore, type 1 reactions to latex proteins may mimic allergic reactions to LAs (64). No study has convincingly demonstrated that latex prick testing should be performed on a routine basis in patients referred with possible allergic reaction to LAs (6, 65).

Diagnostic Methods

Medical history

In two patient series, only 15–37% of patients referred for allergy testing with LAs had a history suggestive of a true allergic event to LAs (4, 53).

When testing is performed in a population with low disease prevalence, a low positive predictive value as well as high proportion of false positive is to be expected. Although a detailed medical history may prevent unnecessary testing, clinical observations and patient interviews are of limited value (16, 23). A careful evaluation should include information about the drug involved, dose, content of preservatives and vasoconstrictors, and a description of the reaction, its onset and duration. An interpretation of the findings and a diagnostic plan should be presented to the patient. Most often, it includes allergy skin testing as well as drug provocation testing but future avoidance of LAs may be chosen. Patients should also be interviewed about previous allergic reactions if a positive patch test reaction to an LA is identified.

Test agents

The aim of skin testing should be to identify one single LA that the patient can rely on in future medical procedures. If a strong anaphylactic reaction is suspected, a drug from a different class of LAs may be used (15). However, in general, the causative drug should be used because anaphylactic reactions are exceptional (6). Lidocaine (or another amide LA) should always be prioritized because its use is widespread and allergic reactions are rare (15). Recommended agents for comprehensive testing of immediate-type immune reactions are tetracaine, mepivacaine, lidocaine and bupivacaine (52). However, national prescription habits should be accounted for, e.g. in Denmark injectable LAs include lidocaine, bupivacaine, ropivacaine, mepivacaine, prilocaine, and articaïne.

Content of preservatives

It has been debated as to whether skin testing should be performed with preservative-free solutions (15, 29, 66). Although parabens are a possible cause of allergic reactions and/or positive skin tests, their role is probably minimal (10). Preservatives may show false-positive reactions upon testing (5, 29, 31, 67, 68). Thus, preservative-free testing may be easier to conclude upon. However, the frequency and availability of paraben-free LAs in the country should be included in the decision. We have found no convincing evidence to determine which approach is superior and, therefore, testing with both paraben-free and paraben-containing LAs may be appropriate in some cases (14). By using such a procedure, a negative test result from testing with a preservative-free solu-

tion (in combination with a positive result from a preservative-containing solution) makes the preservative a likely explanation for the immune reaction. Prick test cannot be performed with solutions containing vasoconstrictors as they mask a local weal and flare reaction (69). Subsequent subcutaneous challenge with vasoconstrictor containing solutions includes only a limited risk in patients without a pre-existing history of sulfite sensitivity (14, 29, 66).

Patch testing

Patch testing should be performed according to the guidelines of the International Contact Dermatitis Research Group (70). The European baseline test series only contains benzocaine, whereas the thin-layer rapid use epicutaneous test (TRUE-test™) system contains a 'caine mix' with benzocaine, tetracaine and dibucaine. The North American Contact Dermatitis Group baseline series includes benzocaine, lidocaine, tetracaine, dibucaine, and prilocaine (71). Ideally, patients suspected of contact allergy to LAs should be tested with prevalent amide and ester group LAs (and parabens and metabisulfite if relevant). The choice should mainly rely on local prescription habits and may, therefore, change over time as new products are introduced (72). In Denmark lidocaine, cinchocaine, prilocaine, cocaine and benzocaine are currently available in topical preparations. Benzocaine, a prevalent constituent of topical preparations such as sunscreens, sunburn relief lotions and haemorrhoid ointments, is a cause of allergic contact dermatitis (51, 73–75). It has been estimated that 5% of individuals who have applied benzocaine will become sensitized to it (76). In 1972, the incidence of contact allergy to benzocaine was 5% in North America (77), whereas the incidence today is considerably lower and comparable with prevalence estimates from Europe (43, 72, 78). It has been stressed previously that patch testing with benzocaine alone may be inadequate and that the inclusion of a 'caine mix' in the European Baseline Series could be beneficial. The single most prevalent cause of lidocaine contact allergy appears to be ointments for pruritus ani (79). However, lidocaine contact dermatitis in Australia is often caused by other over-the-counter lidocaine-containing preparations (e.g. for sunburn relief) (80). The prevalence of contact allergy to lidocaine in North America was 0.7% in the late-1990s (81) and is still uncommon today (82). It was recently suggested that lidocaine should be added to the European standard test series (38).

Prick test and intradermal testing

Prick testing is highly reproducible and no fatalities are known from its use (52). Prick testing is often performed with commercially available diluted (1:100) and then undiluted LAs, but if severe reactions are suspected, 10-fold dilutions (starting at concentrations of 1:1000 or 1:10 000) are used (29, 83). A negative (saline) and a positive (histamine) reference should be included. An intradermal test (IDT) may be used to diagnose both immediate- and delayed-type immune reaction (if readings are performed after 1–2 days) (84, 85). Interpretation is difficult because results may vary depending on temperature, time of day, cleansing of skin, and concomitant drug therapy (7). Both IDT and prick test show false-positive reactions and may prevent the use of easily accessible first-line drugs (Table 2) (3, 10, 23, 86). Such reactions occur because of injection trauma, distension of the skin, localized histamine release from the skin puncture, additives in the solution or from an irritant effect (3, 52). False-positive reactions because of direct histamine release will arise rapidly and fade within 20 min (87) and are mostly observed when skin testing is performed with esters and undiluted solutions (4). False-positive reactions from IDT are not uncommon because 8–41% of controls show positive reactions (3, 14, 29). Similarly, 0–96% (undiluted solution) and 0–36% (diluted solution) patients referred with a history of allergy to LAs may experience false-positive reactions when IDT is performed (Table 2). It should be emphasized that IDT with undiluted solutions have been performed only in a limited number of studies. Wasserfallen and Frei showed positive reactions in 96% of 28 patients (16), whereas the remaining studies showed significantly less positive reactions. The two largest studies showed positive reactions among 10/104 (9.6%) and 10/90 (11.1%) patients (4, 86) and are perhaps closer to a true estimate of the proportion of positive reactions from IDT. Nevertheless, the outcome of IDT with undiluted LA may prove difficult to evaluate and is usually not performed. In a few patients, uneventful drug provocation testing has been carried out despite positive results from previous skin testing (Table 2) (4, 53).

Negative test results are highly reliable (15, 52, 88) although false-negative reactions have been reported (15, 89, 90). An explanation may be that low-molecular-weight drugs are sometimes unable to elicit an allergic response by themselves (53). Instead, drug metabolites or degradation products serve as haptens and bind to protein carriers. However, this has not been shown to occur with LAs and is therefore theoretical. Finally, negative

test reactions may be observed if skin testing is not performed soon after the suspected allergic event because of a decrease in the concentration of IgE (91). This matter has also never been investigated and its clinical relevance is currently unknown.

Subcutaneous challenge (drug provocation test)

A drug provocation test is often performed as it is the gold standard. It is performed as serial subcutaneous injections on an extremity and should always be carried out under strict medical surveillance, whether it is the causative LA, a pharmacologically related LA, or an LA from a different group. General principles for drug provocation testing have been detailed previously (92). Drug provocation testing is unique because it evaluates possible allergic reactions as well as any other adverse reaction irrespective of mechanism. It should be performed following negative skin testing and if there is a clear benefit for the patient. Obsolete LAs should not be tested. Subcutaneous challenge should not be performed in patients with conditions such as severe asthma or underlying cardiac disease and in patients who have experienced life-threatening immunocytotoxic reactions (92). Angiotensin converting enzyme (ACE) inhibitors should be avoided prior to testing because they may aggravate type 1 immune responses (92).

A recommendable test protocol was suggested by Schatz (29), but an abbreviated version using only undiluted LAs can be used. In cases of positive reactions from prick testing or IDT, a different LA should be used (15). Furthermore, only one specific LA should be used for the drug provocation test because this minimizes the risk of anaphylactic reactions. A single-blinded placebo-controlled exposure can be an advantage in cases where psychological aspects are suspected (5). If the patient also reacts to the placebo, a 'reverse placebo provocation' test protocol can be applied (93). Patients with no reactions to the injections should be instructed that the specific LA(s) is considered safe for future injections (7, 94). However, a negative subcutaneous challenge does not absolutely predict future tolerance to LA exposure (16, 65). Table 2 is a tabulation of experience with subcutaneous provocation testing.

In vitro methods

Only a few *in vitro* tests are relevant in the diagnostic approach to patients with suspected type 1 allergies, i.e. the leucocyte histamine release test (21) and the radioallergosorbent test. However, flow cytometric analysis of *in vitro*-activated

Table 2. Previous clinical reports evaluating hypersensitivity to LAs. The list may not be comprehensive

Author	Study year	No. of patients	No. of patients with previous reaction to lidocaine	No. of positive result/no. of patients tested				
				Patch testing	Standard prick testing	IDT (diluted)	IDT (undiluted)	Subcutaneous challenge
Aldrete and O'Higgins (39)	1971	27	—	1/8	—	—	20/27*	0/27
Barnard (99)	1976	20	—	—	—	—	0/20	0/20
Incaudo et al. (53)	1978	71	21/71	—	—	5/59	2/59	0/50†
de Shazo and Nelson (4)	1979	90	—	—	0/90	0/90	10/90	0/90‡
Barer and McAllen (100)	1982	8	—	—	—	2/8	—	0/8
Fisher and Graham (13)	1984	27	27/27	—	—	1/27	0/26	0/27
Le Sellin (101)	1986	25	—	—	0/25	—	—	1/25§
Chandler et al. (23)	1987	59	30/59	—	0/56	—	—	0/59
Ruzicka et al. (86)	1987	104	—	104/104¶	0/104	1/104	10/104	—
Escolano et al. (88)	1990	35	—	—	0/35	1/35	—	0/35
Wasserfallen and Frei (16)	1995	28	11/28	—	4/28	10/28	22/23	0/28
Gall et al. (6)	1996	177	45/177	—	0/177	0/170	—	3/143**
Fisher Bowey (5)	1997	205	—	—	—	3/205	—	0/202
Troise et al. (10)	1998	386	—	—	13/386	3/386	—	0/383
Hein et al. (89)	1999	16	—	—	0/16	0/16	—	0/16
Wildsmith et al. (102)	2000	25	12/25	—	—	1/25	—	0/25
Rood (103)	2000	141	—	—	—	0/141	—	0/44††
Nettis et al. (97)	2001	105‡‡	—	—	0/105	0/105	—	0/105
Astarita et al. (65)	2001	198	—	2/198	0/198	2/198	—	0/198
Macy et al. (67)	2002	252	—	—	2/252§§	1/252	—	0/252
Berkun et al. (66)	2003	236	—	—	0/236	0/236	—	1/236¶¶
Jacobsen et al. (40)	2005	48	29/48	1/48	0/48	3/48	—	0/48
Wohrl et al. (90)	2006	36	—	0/36	—	—	—	1/36***
Gunera-Saad et al. (104)	2007	80	67/80	—	1/80	1/80	—	0/80

IDT, intradermal testing; LA, local anaesthetic; —, not done.

*Procaine = 20/27; tetracaine = 23/27; chloroprocaine = 12/27; mepivacaine = 1/27; lidocaine = 0/27.

†Three IDT-positive patients experienced uneventful subcutaneous provocation with the same LA.

‡Two patients had positive IDT to undiluted 1% procaine but underwent uneventful subcutaneous provocation.

§Subcutaneous challenge with lidocaine led to cough as well as a respiratory deficit (peak flow reduced to 52%). Later, the patient was treated with corticosteroids and antihistamine prior to rechallenge and did not experience any symptoms.

¶Positive patch test reactions to either benzocaine or caine mix. Thirty four of 104 had positive reactions to caine mix, 7/104 to benzocaine and 63/104 had positive reactions to both.

**One patient developed an eczematous reaction and showed positive patch tests to mepivacaine and lidocaine. Two patients developed itchy wheals and erythema that resolved spontaneously within 2 hr.

††Provocation performed intraorally.

‡‡A total 432 subjects were tested but only 105 were referred with an adverse reaction to a LA.

§§Positive reactions only observed against LA with parabens and not reproduced in solutions without parabens.

¶¶The patient developed erythema at the injection site and was later challenged uneventfully with a different LA.

***Elevated heart rate and anxiety from articaine (probably psychogenic).

basophils using CD63 (i.e. the basophil activation test) has been increasingly used to diagnose type 1 allergies. So far, this has not been carried out with LAs but with inhalant allergens, food allergens, latex proteins, and other drugs. In general, the tests do not rule out allergy because their predictive value is not well established. Lymphocyte transformation test may be useful in the diagnosis of delayed-type hypersensitivity (24), but the value of this test compared with the patch test remains to be established.

Conclusions for the evaluation of type 4 allergic reactions

Patch testing should be performed when patients present with contact dermatitis following exposure to topical LAs (Fig. 2). It should also be con-

sidered when patients are referred with localized angioedematous swelling [or even urticaria (24)] following LA injection because it can represent a delayed-type immune reaction (25, 95). In our algorithm (Fig. 2), patch testing has replaced IDT because it is a good predictor of allergic type 4 reactions (65) and because it has a higher sensitivity than IDT (25). If a positive patch test reaction to an ester is observed, a paraben-free amide may be used for future injections without further testing (14). However, if patients have positive patch test reactions to amide LAs, further patch testing should be performed. The test panel should include ester compounds such as benzocaine and tetracaine as well as prevalent amide compounds such as bupivacaine, lidocaine, mepivacaine, prilocaine, articaine and perhaps dibucaine. There is currently no certain pattern of cross-reactivity

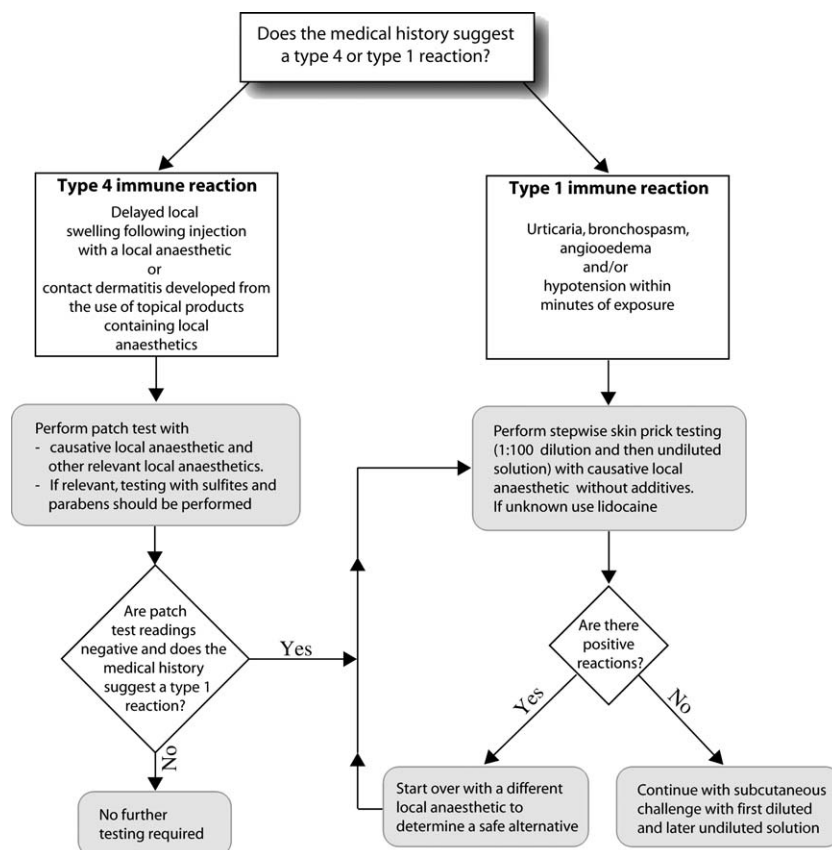


Fig. 2. Evaluation algorithm for patients with a medical history suggesting a hypersensitivity reaction to local anaesthetics.

among various amide LAs (50, 96), but it has been suggested that articaine is a reliable substitute in case of contact allergy to amide LAs (25, 85).

Conclusions for the evaluation of type 1 allergic reactions

The ideal test procedure for immediate-type immune reactions remains a matter of controversy (40). Traditionally, prick testing and IDT have been performed prior to subcutaneous challenge (Table 2) (29). However, evaluation of seven studies with negative allergy skin tests followed by uneventful challenge (4, 6, 16, 23, 65, 67, 97) made Berkun et al., suggest that IDT should be omitted (66). Furthermore, some authors argue that both prick testing and IDT should be omitted from the test protocol because their specificities are low (5, 53). Subcutaneous challenge without prior testing does not pose a risk to the vast majority of patients (Table 2) but may perhaps be an unacceptable risk to a limited number of patients with a true immediate-type immune reaction. As prick testing is inexpensive, quickly performed and may show some diagnostic information in patients with true LA allergy, we suggest it should be performed as it is safe. IDT may be omitted because it is time-consuming and appears to produce more false-

positive reactions than prick test. It should be emphasized that an individual approach is always necessary because no algorithm (Fig. 2) can possibly cover all aspects of this difficult topic.

General Remarks

Hypersensitivity reactions to LAs remain an area of great difficulty. At present, we have no definite information about the pathomechanism behind most immediate-type reactions because specific IgE has proven very hard to identify (12). We believe the proposed algorithm (Fig. 2) accounts for the accumulated knowledge (Table 2) achieved since Schatz proposed his protocol almost three decades ago (15). It recommends that patients are investigated in a setting where both immediate- and delayed-type hypersensitivity immune reactions may be shown as recently proposed (98). Although it may be argued that prick testing should also be omitted because of the rarity of true immediate-type reactions, we believe it is a safety measure in a field of uncertainty.

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