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Hypersensitivity to local anaesthetics

Abstract

Using local anaesthetics in daily practice, particularly by anaesthetists and dentists, is connected with the risk of side effects. Therefore, the observation of side effects, carrying out detailed research (according to the chart proposed in this study) and conducting specialist examinations is of the highest importance. There is a variety of side effects that could occur during local anaesthesia procedures, with the intensity ranging from clinically unimportant to life threatening. Clinicians' major concerns are the appearance of various hypersensitivity reactions, including anaphylaxis. Healthcare providers responsible for the administration of local anaesthetics should be able to detect hypersensitivity reactions to implement appropriate treatment and then choose highly selected diagnostic procedures. The final diagnosis should be based on specific medical history; documentation, including a description of the case and measurement of tryptase activity; skin tests; and provocation trials. Screening tests are not recommended in populations without hypersensitivity to local anaesthetics in their medical history.

Key words: hypersensitivity; local anesthetics; local anesthesia; skin tests

Introducing local anaesthetics into daily clinical practice entirely revolutionized operational procedures. In 1884, Austrian physician Carl Koller successfully superficially anaesthetized the cornea before an ophthalmology procedure. Currently, local anaesthetics are widely used in

many medical fields with different possibilities for application. As they are used more often, as there is an increasing risk of side effects connected with their usage, including hypersensitivity reactions [1]. Usually, adverse drug reactions resulting either from the pharmacological mechanism of action or the intensification of dose-dependent effects are well recognized and therefore predictable. In contrast, hypersensitivity reactions are still disputable, and their diagnosis is a significant challenge for a clinicians. Nevertheless, there has been some progress over the last 2 years. International experts' guidelines attempting to discuss the topic of hypersensitivity to drugs, which is one of the most enigmatic topics in allergology [6], have been published [2–5]. These recommendations also pertain to hypersensitivity reactions against local anaesthetics.

Definitions

The recommendations of Allergology and Anaesthesiology Scientific Societies [2, 4, 7] regarding the management of hypersensitivity reactions to drugs consistently stress the necessity of using proper terminology. This enables efficient communication between clinicians, the reliable performance of research with the precise identification of recruited patients and the ability to compare the results achieved by particular investigators. This aspect is of special importance in clinical trials on unexpected side effects of the drugs, which, for objective reasons, are based mainly on meta-analyses of case reports, as it is difficult to plan randomized, controlled trials in this field.

Adverse drug reactions are connected to qualitatively different responses of organisms, which are often difficult or even impossible to predict, and their appearance and intensity are dose-independent, which should define them as hypersensitivity reactions. The guidelines define them as objective, repeatable symptoms, elicited by exposure to certain drugs, given in doses that are well tolerated by the majority of patients. Allergies to drugs can be diagnosed only in situations where there are documented underlying immunological mechanisms in the development of the following reaction: IgE-dependent or IgE-independent (the most frequent being T cell-dependent). In the remaining cases, with other reasons initiating the symptoms, non-allergic hypersensitivity should be diagnosed.

The most serious form of hypersensitivity, e.g., anaphylaxis, is defined as a severe, life-threatening, general or systemic hypersensitivity reaction. Anaphylaxis is divided into allergic (documented underlined immune mechanisms) and non-allergic (previously defined as anaphylactoid reaction) [8]. Hypersensitivity reactions are also classified as acute (immediate) and delayed (not immediate). This classification does not consider pathomechanisms of the reaction but time since administration of the drug until the onset of clinical symptoms. Immediate hypersensitivity reactions, both allergic and non-allergic, appear between 0 and 6 hours (in rare cases, 6–12 hours but no longer than 24 hours) after the use of local anaesthetics and have similar clinical manifestations (urticaria, oedema angioneuroticum, bronchospasm, rhinitis, conjunctivitis, gastrointestinal symptoms, and anaphylaxis, including anaphylactic shock). Delayed appearance occurs between 24 and 72 hours after exposure (in rare cases after 6 hours) and most frequently manifests with maculopapular rash and delayed urticaria [2].

Epidemiology

The accurate incidence of side effects after local anaesthetics and their underlying mechanisms are difficult to assess. The International Classification of Diseases (ICD-10), which does not involve all aspects of this phenomenon and is mostly directed towards diagnostic information, does not make assessment easier. Not all cases are reported. According to some investigators, hypersensitivity (urticaria/oedema angioneuroticum, anaphylaxis) is the third most common adverse reaction after the use of local anaesthetics [9].

IgE-dependent reactions are the rarest of the adverse reactions. The meta-analysis of all reports published in English-language journals between 1951 and 2011 confirmed the incidence of such cases (documented based on diagnostic procedures) among patients with suspicion of hypersensitivity to local anaesthetics to be 1% [10]. Cell-mediated allergic reactions are more common and are accompanied by primary symptoms of non-allergic hypersensitivity [11]. However, the majority of side effects, with some resembling hypersensitivity reactions, are connected with other causes such as toxicities, the effect of concomitant administration of adrenaline, vasovagal collapse, and a fear response or hyperventilation syndrome [10, 12].

Management of hypersensitivity to local anaesthetics

According to the World Allergy Organization (WAO), unexpected side effects during anaesthesia should be clarified; therefore, they have an indication for intensified diagnostics and consultations with specialists, including allergologists (Figure 1 presents the proposed management algorithm). Local anaesthetics are essential to perform many procedures and cannot be eliminated without resolving doubts about their tolerance (which is a tactic suggested by some authors) [13, 14].

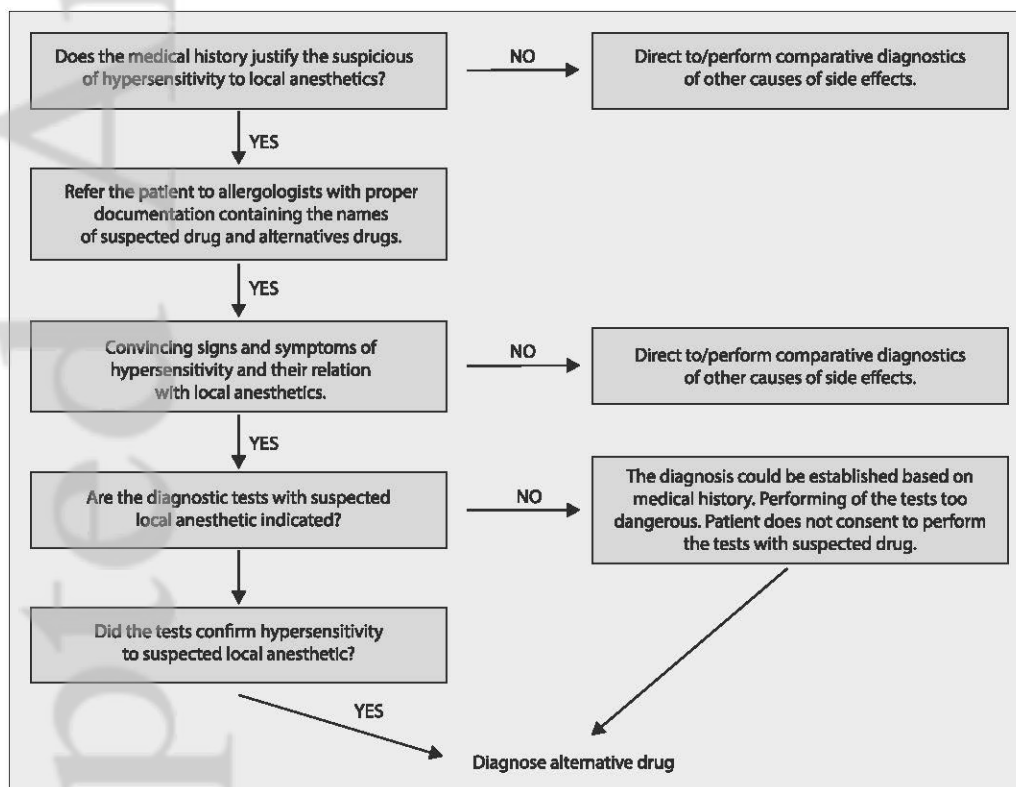


Figure 1. Management algorithm in case of suspicious of hypersensitivity to local anesthetics

The diagnosis of unexpected side effects during local anaesthesia is a difficult task. These signs and symptoms do not necessarily indicate a hypersensitivity to local anaesthetics. Thus, the role of collaboration between allergologists (who have the preparation and knowledge needed to diagnose hypersensitivity) and anaesthesiologists (who have the most experience in evaluating

anaesthetics' side effects, resulting from their pharmacological as well as toxic features) is crucial [7].

1. Until the aetiology of unexpected side effects is identified, the term “hypersensitivity to local anaesthetics” should be used

When a patient currently presents or has previously presented signs and symptoms suggesting an allergy to local anaesthetics, until the underlying mechanisms are clarified, it is recommended to use in verbal and written communication the term “hypersensitivity to local anaesthetics”. A preliminary diagnosis of hypersensitivity to local anaesthetics (in the case of unexpected side effects) is justified from not only a factual but also a practical point of view. The physician referring the patient to an allergologist is not obligated to verify whether the causes of the symptoms are immune (allergic hypersensitivity) or non-immune (non-allergic hypersensitivity) mechanisms. For objective reasons, the diagnostics of hypersensitivity should be wider than an allergy to local anaesthetics alone. It is important for the patient not to use the term “allergy” during contact with physicians until it is finally confirmed. Doing so could lead to a bias, and patients' reports about allergies might be wrongly assessed as an allergy to a particular drug. Clinical practice shows that in some patients, certain drugs are avoided for many years based exclusively on vasovagal symptoms, which is why the physician's description of the episode is so important and should be included in the discharge documentation given to patients when they are referred for further diagnostics, as described below.

2. The physician administering the anaesthetic or taking care of the patient during the occurrence of side effects should make every effort to explain those reactions [7].

These actions should cover a reliable description of the event included in the discharge documentation as well as in a referral for a consultation with a particular specialist together with the attached medical documentation.

Information that should be included in the patient's documentation is as follows:

a) Information regarding the drug suspected of causing the hypersensitivity reaction.

The trade name; route of administration; dose, date and time of administration; and previous tolerance of this drug or other drug from this group if used before should be included in the information.

b) Information regarding the hypersensitivity reaction.

The date and time of the symptoms' occurrence, together with their duration; a detailed description of signs and symptoms with special consideration of the targeted organ or system (including a photo if justified); management; and diagnostic workup, including laboratory tests, should be included.

Monitoring tryptase activity is especially helpful during comparative diagnostics of the causes of side effects (particularly when anaphylaxis is suspected). Taking a blood sample three times is recommended: directly after symptom occurrence and then 1 and 2 hours thereafter, as well as 24 hours after resolution (not resulting in the delay of therapy). To do so, 5–10 mL of blood should be taken (for the clot) and centrifuged, and the serum should be refrigerated (if the evaluation is possible within the next 48 hours) [7] or frozen at a temperature of -20°C [16]. Increased activity of tryptase suggests anaphylaxis or another hypersensitivity reaction with the degranulation of mastocytes. The highest values are observed between 60 and 90 minutes after first symptoms, and then after 6 hours, activity should normalize, with baseline values achieved usually after 24 hours (baseline activity). Tryptase activity within the normal range does not exclude anaphylaxis, but its increased value could retrospectively support the diagnosis. Unfortunately, despite guidelines recommending monitoring tryptase activity in each suspected case of hypersensitivity reaction, these tests are too rarely performed.

In some cases with skin manifestations of hypersensitivity, the skin biopsy can be taken for histological examination.

c) Additional information

The trade names of any other drugs, administered concomitantly with “suspected” local anaesthetic, should be included.

Concomitant diseases and medical conditions, including allergic diseases, as well as signs and symptoms of infection should also be included. For example, dyspnoea reported by the patients could be a symptom of asthma existing for many years.

Information about all previous suspected hypersensitivity reactions to the drugs should be included.

3. Is allergology consultation necessary before the use of local anaesthetics?

The current level of knowledge does not allow predicting which patient will present a hypersensitivity reaction to local anaesthetics. The only risk factor of a similar or even more severe reaction after the second exposure to local anaesthetics could be the past appearance of unexpected side effects after those drugs. Therefore, a detailed medical history regarding previous tolerance to local anaesthetics could be the basis for making a decision about using a certain drug or referring the patient to an allergologist. The evaluation of the patient before anaesthesia should also include the tolerance of other concomitantly administered drugs (preservatives, antiseptic preparates, non-steroidal anti-inflammatory drugs [NSAIDs], and antibiotics), as well as the materials and equipment with which the patient could have contact during the procedure.

A medical history showing previous hypersensitivity reactions connected with local anaesthetic administration should be included in the abovementioned medical documentation and should result in a consultation with a specialist. Additionally, an allergological consultation confirming hypersensitivity to certain local anaesthetics should also indicate alternative drugs that are safe for the patient. Patients without such documentation should be referred for an allergological consultation before the use of a local anaesthetic [17]. Referral documentation should be accompanied by a detailed description of the event and information about the planned use of a local anaesthetic with the name of the drug (first and second alternatives), as sometimes allergologists receive referral documentation with only a diagnosis of “allergy to the drugs” and with a request to perform “tests for the specified drugs”.

The medical history is an important part of the allergological diagnostic procedure, taking into consideration the detailed description of the event, which could be suggestive enough that allergologists would consider performing the test for this drug to be too dangerous and

redundant. If there is no doubt regarding the causative relationship between anaphylaxis symptoms and certain drugs, initiation of the diagnostic from the assessment of tolerance to alternative drugs could be allowed.

The retrospective evaluation of signs and symptoms based only on data from the patient's medical history could be biased due to the time that has passed since the event. Moreover, patients are unable to present the majority of information necessary for a full allergological evaluation. Therefore, a detailed medical history is of the highest importance, but the clinician's description of the event is also crucial, including information compatible with point 2 of the questionnaire proposed by the *European Network for Drug Allergy (ENDA)* [18]. Physicians administering anaesthetics or caring for the patient during the occurrence of side effects connected to the drug should enclose full documentation containing the abovementioned information when referring a patient for an allergological consultation.

4. Allergology procedures

a) Skin tests

Skin tests are an important part of diagnosing allergic hypersensitivity to drugs.

Nevertheless, in many cases, they have limited diagnostic value considering the lack of standardized levels for their performance or unknown predictive value of the results. However, for local anaesthetics, there were defined concrete optimal levels for performing skin tests, and negative results have a predictive value of up to 97% [19]. Thus, the evaluation of allergic hypersensitivity to local anaesthetics could have a practical importance, as it could either confirm or exclude allergies to local anaesthetics [5]. To perform the tests, commercially available preparates are used that do not contain adrenaline or other ingredients such as sulfites or parabens [20]. The following tests are used: skin prick tests (SPT), intradermal tests (IDT), and patch tests (PT).

Prick tests have a higher specificity but a lower sensitivity. They are connected with a lower risk of anaphylaxis at each time point during the procedure. The use of a non-diluted local anaesthetic solution is recommended to perform these tests (strong recommendation/high quality of evidence according to GRADE, *Grading of Recommendations Assessment, Development and Evaluation* [5, 21]).

Intradermal tests are more sensitive and repeatable but have lower specificity and are connected to a higher risk of side effects. They are performed only after negative results of an SPT. Local anaesthetic drugs are used at a dilution of 1: 10 (strong recommendation/high quality of evidence according to GRADE [5]). It is recommended to perform the test with gradually increasing concentrations (1: 100, 1: 100, 1: 10), which decreases the risk of serious side effects [2].

Prick tests and intradermal tests detect IgE-dependent mechanisms. However, diagnosis of hypersensitivity to local anaesthetics should not be limited entirely to immediate reactions because in some patients, delayed reactions can also be detected. For this reason, the patient should be advised to observe the region of skin in which the tests were performed for a prolonged time and to promptly inform the physician of any changes. Brockow *et al.* [5] recommend intradermal tests with local anaesthetics at a dilution of 1: 10 to assess delayed allergic reactions along with patch tests. The delayed assessment of IDT results (measurement of the infiltration diameter after 48 hours) compared to patch tests is of comparable or even higher sensitivity in the diagnosis of those reactions.

Prick tests are performed with undiluted prepare (strong recommendation/high quality of evidence according to GRADE [5]). They allow the diagnosis of cell-mediated hypersensitivity and are helpful in the diagnosis of contact allergies to local anaesthetics. The purpose of performing of patch tests with local anaesthetics has been stressed [22]. Cell-mediated hypersensitivity is common while using ester compounds but is also possible with the use of amide derivatives [23]. After using benzocaine to decrease soreness at the injection site, symptoms of contact allergies could develop that are sometimes judged erroneously to be inflammatory infiltrates [24, 25].

b) Provocative tests (single-blind, placebo controlled)

Hypersensitivity to local anaesthetics is diagnosed independently of its mechanism using provocative tests. These are used to diagnose non-allergic hypersensitivity and to confirm tolerance of local anaesthetics indicated in skin tests. They should be always performed along with choosing an alternative drug (strong recommendation/high quality of evidence according to GRADE [5]). Provocative tests with drugs are performed only if the possible benefits outweigh the risks connected to them. The latter situation concerns local anaesthetics because local

anaesthesia is used in many medical procedures [5]. The test is performed with the single-blind method (the patient is not aware whether he or she is being given a local anaesthetic or placebo) to exclude unspecific or psychogenic reactions. The test begins with saline administration and then 0.1, 0.2, 0.5, 1.0, and 2.0 mL of undiluted local anaesthetic (without adrenaline) is given subcutaneously on the extensor forearm surface at the width of a hand over the elbow joint with time intervals of 30 minutes between injections [26]. Patients should be informed in detail about the aim of the test and connected risks as well as about the details of the procedure and placebo usage and then should provide written informed consent.

All guidelines unanimously emphasize that provocative tests should be the last step of diagnosis upon negative results of skin tests. However, if allergological diagnosis cannot be conducted and there is some doubt pertaining to the medical history, it is possible to perform provocative tests with an alternative drug without skin tests [27]. In these cases, undiluted local anaesthetic is administered subcutaneously (without adrenaline) in doses between 0.5 mL and 1 mL. Lack of a hypersensitive reaction within 30 minutes since the injection is considered to be a negative result [16].

If symptoms occur during placebo administration, a reverse provocative test with placebo can be used, the 4 consecutive stages of which are presented in Table 1.

Table 1. Reverse placebo provocation test [2, 26]

Procedure performed	Information given to the patient	Result of provocation	Recommended proceeding
Injection of local anaesthetic	Injection of local anaesthetic	Patient reports complaints	Continuation of procedure
Injection of saline	Injection of the next dose of local anaesthetic	Patient reports complaints	Continuation of procedure
Injection of local anaesthetic	Injection of placebo	Patient does not report complaints	Continuation of procedure
		Patient reports complaints	Positive result of provocation test

Injection of local anaesthetic	Informing the patient about previous procedures and then injection of local anaesthetic	Patient does not report complaints	Negative result of provocation test
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Where, when and in whom are diagnostics performed?

Diagnostic procedures (even skin prick tests, which are considered the safest) should be performed by experienced allergologists or in specialized sites using the typical precautions for allergological procedures.

Allergological diagnostics should be performed in patients in whom hypersensitivity symptoms have occurred within 4 weeks up to 6 months after their resolution and the cessation of anti-allergic treatment. After this period, the results will be less credible. It has been shown that sensitivity to skin tests with the drugs declines over time [2].

An allergological evaluation should also be ordered in the case of elective surgical procedures with local anaesthesia in patients who showed symptoms of hypersensitivity in the distant past but do not have any documentation supporting that event to indicate the drugs that are safe within this group. The previous anaesthesiologist should make every effort to obtain the information regarding the previous anaesthesia and deliver this information to the current anaesthesiologist [17].

If clinical signs and symptoms of hypersensitivity during local anaesthesia were unambiguous and the diagnostics were negative, a second diagnostic is recommended after approximately 4-6 weeks. The reason for this procedure is a suspicion that reactivity to local anaesthetics decreases with time but that performing diagnostics could reactivate a state of hypersensitivity (the booster effect).

In contrast, performing the above diagnostic procedures is not indicated in patients without hypersensitivity symptoms after the use of local anaesthetics in their medical history [2]. This also applies to patients with asthma and other atopic diseases and to patients with allergies to

substances or drugs to which they will not be exposed during operation. Additionally, patients with mastocytosis who are particularly predisposed to anaphylaxis (especially drugs) also do not comprise the group with the risk of side effects after local anaesthetics. There are only single case reports of hypersensitivity to local anaesthetics described in this group thus far, despite the fact that every patient from this group undergoes bone marrow aspiration during general anaesthesia. Taking into consideration the lack of such cases, it is believed that the risk of hypersensitivity to local anaesthetics in patients with mastocytosis is not higher than in the general population [3].

Allergological diagnostics are also not useful in cases of side effects resulting from pharmacological and toxic features of local anaesthetics.

Cross-reactivity

Each case of documented hypersensitivity to a particular drug leads to the necessity of assessing whether there is a cross reactivity with other local anaesthetics available on the market as well as the obligation to identify alternative safe drugs. Good tolerance of the alternative drug should be confirmed not only based on negative results of skin tests but also on the results of provocative tests. On the contrary, assuming cross reactivity without documentation during diagnostics is a mistake. Cross reactions are typical for ester forms but are uncommon for amide derivatives. There are cases of allergic reactions to lidocaine with a good tolerance of articaine [28] or symptoms of urticaria connected only to mepivacaine but with a lack of side effects after lidocaine and bupivacaine [29]. However, there are also cases of documented concomitant allergy to a few preparates of amide derivatives [30]. The most common is cross reactivity between lignocaine and mepivacaine [31].

Good tolerance to alternative local anaesthetics in provocative tests (with hypersensitivity to others) does not justify excluding the participation of this drug in unexpected reactions that could possibly have occurred in the past. In such situations, premedication could be considered (the administration of glucocorticosteroids and anti-histaminic drugs), which is more effective in the prevention of symptoms of non-allergic hypersensitivity than in IgE-dependence (with symptoms that more commonly concern local anaesthetics) [4].

Other causes of hypersensitivity reactions during local anaesthesia procedures

Local anaesthesia procedures are connected with hypersensitivity not only to anaesthetics but also to the preservative additives contained in particular drugs (parabens, sulfites) as well latex and nickel or antiseptic preperates [32, 33]. Nickel can be released and absorbed in organisms from needles used for injections, and the potential sources of latex are mainly vials and cartridges containing local anaesthetics and syringes with latex caps and gloves. Preservative additives could be a cause of anaphylaxis or delayed reactions. Some reports indicate the significant participation of allergies to methylparaben in the development of hypersensitivity symptoms during local anaesthesia [10, 34]. Thus, diagnostics of the reactions to preserving additives if symptoms of hypersensitivity occurred after the administration of local anaesthetics containing them is recommended (consequently, the trade name of the local anaesthetic is essential information that should be delivered to the consulting allergologists). Additionally, it has been stressed that during the diagnosis of hypersensitivity to sulfites, only oral provocative tests are recommended (strong recommendation/moderate quality of evidence according to GRADE) because both positive and negative results of skin tests have a low predictive value [5].

Summary

Although hypersensitivity reactions account for a minority of all reported side effects after the administration of local anaesthetics, they are proportionally frequent to the use of these drugs. Physicians using local anaesthetics should know how to diagnose signs and symptoms of hypersensitivity and how to introduce appropriate treatments and initiate any activities that could allow the performance of proper diagnostics in the future. According to the recommendations, a detailed description of the event is of the highest importance [2]. The occurrence of unexpected side effects during previous anaesthesia is the most important factor of their development after local anaesthetics. Even with previous good tolerance of local anaesthetics, strong vigilance is warranted because a hypersensitivity reaction could occur during the next exposure. A comprehensive diagnosis of hypersensitivity to local anaesthetics should consider the data from objective documentation and also involve tests, allowing the assessment of immediate and

delayed reactions, not only to local anaesthetics but also to the ingredients of the prepartate and other issues connected with anaesthesia [35].

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