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Research Paper

Allergic Reactions to Local Anesthetics – Observational Study

Medical Science

KEYWORDS : allergy, local anesthetics, anaphylactic reactions

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ABSTRACT

To analyze the spectrum of adverse reactions to local anesthetics. Twenty consecutive patients due to severe reaction observed after administration of local anesthetic.

Skin prick tests, intradermal tests, and progressive provocation challenge with suspected local anesthetic and its commercially available replacers were conducted 4 weeks to 2 months following the episode of post-drug reaction.

The list of suspected local anesthetics included lidocaine (n=11), mepivacaine (n=4), articaine (n=3), bupivacaine and tetracaine (n=1 each). The safety of mepivacaine was confirmed in 5/7, bupivacaine in 6/7, and lidocaine in only 1/3 tested subjects. One mepivacaine-sensitive individual and one patient sensitive to lidocaine further proved tolerant to bupivacaine. One subject with bupivacaine hypersensitivity showed tolerance to mepivacaine. There were six cases of cross-reactivity between various anesthetic agents.

Comprehensive evaluation of potential hypersensitivity to LA should include analysis of patient history and medical documentation, testing for immediate reaction to a given anesthetic preparation, as well as cross-reactivity testing.

Introduction

Allergic reactions to local anesthetics (LAs) are extremely rare. It is estimated that they constitute less than 1% of all immediate hypersensitivity reactions to anesthetic agents.[1,2] Fisher and Bowey[3] studied the prevalence of allergic reactions to LA in a group of 208 patients; they documented four cases of immediate hypersensitivity and another four patients with delayed-type reaction. Adverse reactions have been associated with LA use, since early years.Vasomotor reactions, toxicity resulting from inadvertent intravenous injection, symptoms caused by adrenaline, parabens or sulfates used as preservatives of LA preparations, or latex and nickel, were the majority of the adverse reactions.[4,5] Nickel can be released from injection needles, whereas potential sources of latex include vials and containers with LA, syringe tips, and gloves. LAs can also exert sympathetic effects, such as tachycardia, headache, or syncope. Among two widely used groups of LAs, esters of para-aminobenzoic acid (PABA) constitute the main source of potential allergens while amide anesthetics virtually lack immunogenic properties.[6] Delayed-type hypersensitivity (type IV hypersensitivity), i.e. contact dermatitis, is the most frequent response to LA.[7]

The LA-induced anaphylactic reactions of various severity (grade 0 to IV) constitute frequently underdiagnosed perioperative complication.[8] The initial signs of IgE-dependent response can be observed up to 30 minutes upon LA administration. The most frequent are skin lesions; they can be accompanied by respiratory, alimentary, and cardiovascular symptoms, leading to life-threatening anaphylactic shock.

The aim of this study was to analyze the spectrum of adverse reactions to LA with an aid of our original strategy of identifying immediate hypersensitivity to local anesthetics.

Methods

The study, conducted between 2004 and 2009, included twenty case series involving 2978 patients who were referred to our department by their doctor or dentist due to severe reaction observed after administration of LA. The study was approved by The Szczecin Medical University Ethics and Research Committee and signet informed consent for the procedures and publication of data ensuring confidentiality was obtained from all subjects. Mean age of the participants was 49±17.75 years, and their body weight amounted 65.58±10.14 kg. Twelve patients had a history of various allergies: to antibiotics (cephalosporins and penicillins), dust mites, animal fur, and foods (fish, eggs, and milk). The spectrum of previously experienced post-drug reactions included urticaria (n=5), cardiovascular symptoms (n=2; tachycardia and hypertension), and neurological symptoms (n=2).

The patients were examined 4 weeks to 2 months following the episode of post-drug reaction. Detailed history was collected, followed by comprehensive allergological evaluation. Initially, the patients were tested with a LA which caused previous episode of post-drug reaction. If hypersensitivity to the LA was objectively confirmed (positive results of skin tests and progressive provocation test, and negative result of provocation with placebo), other commercially available LAs used for a given type of anesthesia were tested to identify a safe anesthetic and exclude potential cross-reactivity.

Skin tests were always preceded by the insertion of intravenous catheter and were performed under conditions enabling the implementation of intensive therapy whenever necessary. The protocol of the tests and the interpretation of their results followed the European Academy of Allergology and Clinical Immunology (EAACI) guidelines. The procedure begun with skin prick tests (SPTs), in the case of negative or indeterminate result followed by intradermal tests (IDTs). The results of SPTs were read after 15 and 30 minutes, and interpreted against negative (0.9% NaCl) and positive control (histamine/codeine). The presence of blister with diameter larger than 3 mm and surrounding erythema, and the lack of reaction to control 0.9% NaCl were considered as the positive result of the test. In the case of IDT, the examined allergen was injected intradermally twice with 20 minute interval in between. More than 3 mm difference in the diameter of blisters corresponded to the positive result of the test.

The hypersensitivity to LA was ultimately excluded on the basis of the negative result of blinded provocation test. During the challenge, patients were administered increasing doses/concentrations of examined agent at 20-30 minute intervals, according to the protocol presented in Table I. In the case of the positive result of the provocation, a challenge with placebo was conducted on the other day to exclude the false-positive result of the testing.

Table I. Protocol of progressive provocation with local anesthetic

Dose	Volume (ml)	Dilution
I	0.1	1:100
II	0.1	1:10
III	0.1	1:1
IV	0.5	1:1
V	1.0	1:1

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Additionally, the serum levels of specific IgE against latex and penicillin were determined in all patients (Cap-RAST, Pharmacia; Alastat Diagnostic Product Corporation). The titer higher than 0.35 KU/l was considered as the positive result.

Results

All twenty patients remembered the name of LA suspected of previous episode of post-drug reaction, or it could be extracted from their medical documentation. The list of potentially harmful agents included preparations of lidocaine (n=11), mepivacaine (n=4), articaine (n=3), bupivacaine and tetracaine (n=1 each).

Most subjects (19/20) had a history of objective symptoms consistent with hypersensitivity and toxic reaction: loss of consciousness, hypotonia, arrhythmia, erythema, swelling, chills, muscle tremor, seizure, speech and visual disorders (13/20), or at least showed subjective signs suggesting adverse drug reaction (ADR): weakness, sleepiness, anxiety, heart palpitation, throat tightness, dyspnea (6/20). These manifestations were observed up to 30 minutes upon administration of suspected LA.

Skin tests, progressive provocation, and the lack of reactivity to placebo confirmed hypersensitivity to the suspected LA in 17/20 subjects. Hypersensitivity to mepivacaine was excluded in two individuals: one with a history syncope and transient loss of consciousness during a dental procedure, and another one who experienced thrills and fever upon dental anesthesia. Moreover, we did not confirm hypersensitivity to bupivacaine in one female patient who had a history of hypotension with associated arrhythmia in the form of ventricular extrasystole during cesarean section under subarachnoid anesthesia. The remaining 17 individuals with documented hypersensitivity to one LA required identification of another, safe agent.

The safety of mepivacaine was tested in seven patients. Five of them showed tolerance to this agent. In another two patients, the administration of mepivacaine caused subjective symptoms, not observed upon the administration of placebo. Subsequent testing with bupivacaine confirmed good tolerance to this agent in one patient. Another subject experienced subjective symptoms of bupivacaine hypersensitivity, and therefore was excluded from further identification of a safe LA (Fig. 1).

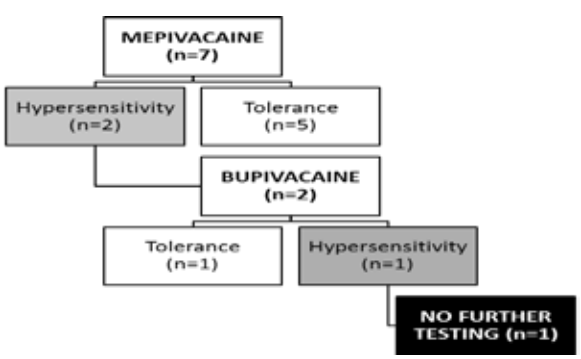

Fig. 1 Flow-chart of mepivacaine tolerance testing

Six out of seven tested patients showed tolerance to bupivacaine. One individual developed skin reaction and had subjective complaints (sore throat) after intradermal administration of this agent. Five minutes after subsequent challenge with bupivacaine, the patient reported progressive deterioration of condition, and weakness. Additionally, pallor of the skin and sweating were observed. A decrease in arterial blood pressure was noted, from 110/70 to 80/50 mmHg, along with a slight increase in heart rate, from 80 to 125 beats per minute. The symptoms resolved upon administering 500 ml 0.9% NaCl in a fast intravenous infusion, and no adrenaline was required. The result of provocation with placebo conducted on the other day was negative. Subsequent mepivacaine challenge proved good tolerance to this agent (Fig. 2).

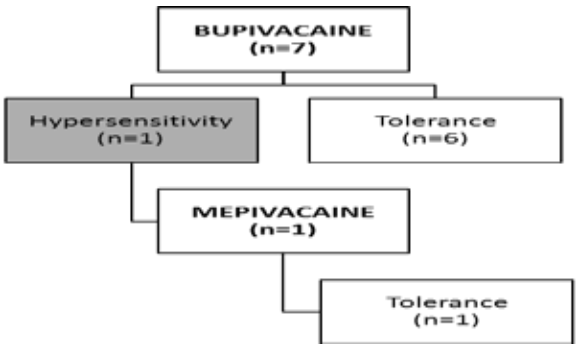

Fig. 2 Flow-chart of bupivacaine tolerance testing

Tolerance to lidocaine was confirmed in only 1 out of 3 tested patients. One patient showed severe neurotoxicity upon administration of 0.2 ml 1% lidocaine, and required hospitalization at ICU. Psychogenic origin of symptoms was excluded during later provocation with placebo, and further attempts to identify a safe LA were discontinued. The third patient had positive results of IDT with lidocaine at 1:10 000 to 1:100 dilution. Urticaria of the chest skin with simultaneous itching was noted during the intradermal testing. Further testing proved tolerance to bupivacaine in this individual (Fig. 3).

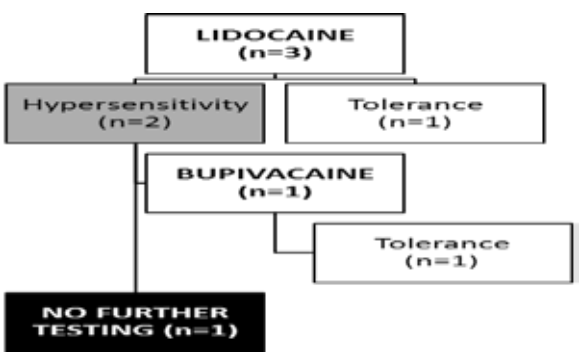

Fig. 3 Flow-chart of lignocaine tolerance testing

Overall, we identified a safe LA in 15 out of 17 tested individuals. Noticeably, there were six cases of cross-reactivity between various anesthetic agents. None of the patients had specific IgE against latex and penicillin.

Discussion

Our experiences suggest that administration of LA is rarely associated with immediate hypersensitivity. Although the course of hypersensitivity reactions is usually unexpected, it has potentially important clinical implications. Therefore, proper evaluation of patients at risk of anaphylactic reaction is vital for both treatment and prevention. History taking and comprehensive analysis of medical documentation constitute initial vital step of correct diagnosis. Also clinical signs reported by the patient and observed during administration of LA or thereafter should be analyzed carefully. Each patient with a history of previous hypersensitivity to LA should be referred to allergology consultation in order to perform targeted skin tests and identify anesthetic agent which could be used during potential surgeries in future. LA used for skin tests should not contain preservatives or adrenaline as they both can alter skin responsiveness. Noticeably, pos-

itive result of SPT can be also obtained in healthy subjects and does not necessarily correspond to IgE-dependent immediate reaction. Nevertheless, the skin tests should be always considered during evaluation and diagnosis of potential hypersensitivity to LA. Provocation with suspected agent is unavoidable in some suspected cases. However, such challenges are associated with considerable risk and therefore should be always conducted in a hospital setting. Controversies associated with the use of provocation tests result from unknown determinants of adverse reactions to LA and not always obvious character of symptoms.

Plausibly, most ADRs which caused referral of our patients resulted from inadvertent intravascular administration of LA, leading to its excessive blood concentration and systemic reaction. This was associated with hypotension, and not infrequently caused transient loss of consciousness. Also other factors which can mimic hypersensitivity (toxicity, vasovagal syncope, anxiety, and hyperventilation syndrome) should be considered in the evaluation of ADR associated with LA administration. Serum samples for mast cell tryptase (MCT) should be obtained in indeterminate cases, optimally two hours following the manifestation. Elevated level of MCT can prompt retrospective diagnosis of anaphylaxis; however, it does not distinguish between allergic and non-allergic hypersensitivity as MCT is a marker of both immune- and non-immune-mediated mast cell degranulation. MCT is considered as an optimal marker of anaphylaxis.[9,10] However, the negative result of MCT testing does not substantiate discontinuation of diagnostic process. This in particular refers to the cases in which the blood was obtained too early in the course of the reaction, or in the case of weak, grade I or II, reactions. The rule that anaphylaxis should not be diagnosed on the basis of a single test seems particularly reasonable.

Adverse reaction to LA can also result from addition of adrenaline or preservatives: sulfites and parabens.[11,12] Adrenaline is frequent additive of LA, and can cause adverse effects (heart palpitation), especially if anesthetic agent was administered in the region of rich-vascularized mucosa. Hypersensitivity to sulfites, inorganic antioxidants which are widely used as preservatives in food and pharmaceutical industry, is another important issue. Noticeably, a history of sensitivity to certain foods can suggest allergy to sulfites. Parabens are rarely used as preservatives of LA; however, the metabolites of methylparabens and propylparabens are structurally similar to PABA, being a potent allergen.[11] Allergy to latex should be also considered as a differential diagnosis of post-LA ADR. However, we did not identify any cases of this allergy amongst our patients.

Discussing issues of sensitivity to LA, one should distinguish between the esters of PABA (procaine, tetracaine) and acid amides (e.g. lidocaine, bupivacaine, articaine, mepivacaine). The esters of PABA are postulated to sensitize more frequently than the amides.[6] Moreover, cross-reactivity can be expected in this former group, at least in the case of contact allergies.[13] Therefore, whenever hypersensitivity to PABA derivatives is supposed, one should exclude sensitivity to both the suspected LA and other structurally-related agents.[14] While the therapeutic concentrations of ready-to-use PABA esters can be used during SPTs, 1:10 dilutions are recommended during IDTs to avoid signs of irritation.[1]

Searching through available literature we did not find any evidence supporting the lack of cross-reactivity between amide LAs. In contrast to previously published reports, recent findings suggest that amides can cross-react with each other.[15] Using the experience-based algorithm of finding safe LA, we revealed six cases of cross-reactivity between amides: lignocaine, mepivacaine, and bupivacaine. This finding seems important in the context of treatment quality and patient safety. Noticeably, one of our mepivacaine-sensitive patients presented signs raising suspicion of cross-reactivity to lidocaine upon progressive provocation with 0.2 ml of this LA, and required hospitalization at ICU.

Due to small number of examined cases, the hereby presented procedure of identifying safe LA should be considered a clinical experience-driven rather than an evidence-based evaluation method. Nevertheless, we postulate its use in patients suspected of sensitivity to LAs as early identification of causative factor and potential cross-reactants is vital in the case of patients at risk of life-threatening anaphylaxis.

In conclusion, our study confirmed that comprehensive evaluation of potential hypersensitivity to LA should include analysis of patient history and medical documentation, testing for immediate reaction to a given anesthetic preparation, as well as cross-reactivity testing.

REFERENCE

1 Amsler E, Flahault A, Mathelier-Fusade P, Aractingi S. Evaluation of re-challenge in patients with suspected lidocaine allergy. Dermatology 2004; 208:109-111. | 2 Finucane BT. Allergies to local anesthetics - the real truth. Can J Anaesth 2003; 50:869-874. | 3 Fisher MM, Bowey CJ. Alleged allergy to local anaesthetics. Anaesth Intensive Care 1997; 25:611-614. | 4 Parkes AW, Harper N, Herwadkar A, Pumphrey R. Anaphylaxis to the chlorhexidine component of Instillagel: a case series. Br J Anaesth 2009; 102:65-68. | 5 Thyssen JP, Menne T, Elberling J, Plaschke P, Johansen JD. Hypersensitivity to local anaesthetics--update and proposal of evaluation algorithm. Contact Dermatitis 2008; 59:69-78. | 6 McLure HA, Rubin AP. Review of local anaesthetic agents. Minerva Anestesiol 2005; 71:59-74. | 7 Khan DA, Solensky R. Drug allergy. J Allergy Clin Immunol 2010; 125:S126-137. | 8 Tryba M, Ahnefeld FW, Barth J et al. Akuttherapie anaphylaktoider Reaktionen. Ergebnisse einer interdisciplinären Konsensuskonferenz. Allergo J 1994; 3:211-224. | 9 Baldo BA, Pham NH, Zhao Z. Chemistry of drug allergenicity. Curr Opin Allergy Clin Immunol 2001; 1:327-335. | 10 Fisher MM, Baldo BA. Mast cell tryptase in anaesthetic anaphylactoid reactions. Br J Anaesth 1998; 80:26-29. | 11 Eggleston ST, Lush LW. Understanding allergic reactions to local anesthetics. Ann Pharmacother 1996; 30:851-857. | 12 Simon RA, Stevenson DD. Adverse reactions to food and drug additives. In: Middleton EJ, Reed CE, Ellis EF, Adkinson NFJ, Yunginger JW and Busse WW (editors) Allergy Principles and practice 4th Ed. St. Louis: Mosby, 1993. | 13 Fuzier R, Lapeyre-Mestre M, Mertes PM et al. Immediate- and delayed-type allergic reactions to amide local anesthetics: clinical features and skin testing. Pharmacoepidemiol Drug Saf 2009; 18:595-601. | 14 Michalska-Krzanowska G, Kurek M. Reakcja neurotoksyczna na niską dawkę lidokainy podaną w teście progresywnej prowokacji. In: Stany nagle w alergologii: Medical Tribune, 2004: 157-161. | 15 Schatz M. Skin testing and incremental challenge in the evaluation of adverse reactions to local anesthetics. J Allergy Clin Immunol 1984; 74:606-616. |