



Contents lists available at ScienceDirect

Allergology International

journal homepage: <http://www.elsevier.com/locate/alit>

Letter to the Editor

Immediate-type allergic reactions to local anesthetics

Dear Editor,

Adverse reactions to local anesthetics are frequently reported, but true allergic reactions are very rare.^{1,2} Adverse reactions are commonly related to vasovagal reactions, dose-related toxic effects, and the side effects of epinephrine within local anesthetics.³ Usually, skin prick tests and intradermal tests of potential causative agents are performed to diagnose allergies. Evaluations of allergic reactions to local anesthetics based on such skin tests have been reported previously.^{1,2} Recently, the number of drugs containing local anesthetics, including over-the-counter medicines, has increased. Therefore, the number of individuals that have become sensitized to local anesthetics might have increased. However, there are few recent reports about allergic reactions to local anesthetics. Thus, we investigated our recent results of skin test reactions to local anesthetics.

We conducted a retrospective study of the cases of 67 patients (16 males, 51 females; median age: 51 years; range: 19–90 years) who suffered adverse reactions to local anesthetics and underwent skin tests between January 2008 and December 2015 at the Department of Dermatology, University Hospital, Kyoto Prefectural University of Medicine. The study protocol was approved by the university ethics committee and was conducted in accordance with the Declaration of Helsinki. The skin tests of local anesthetics included skin prick tests, intradermal tests, and subcutaneous challenge tests. The skin prick tests were performed with 1:1000, 1:100, and 1:10 diluted solutions and undiluted solution, together with positive (histamine dihydrochloride; 10 mg/ml; Wako Pure Chemical Industries, Osaka, Japan) and negative (saline) controls. Wheals were measured at 15 min after the application of the test solution. A positive response was recorded when the mean wheal diameter was more than half of that of the positive control. Intradermal tests were carried out with 1:1000, 1:100, and 1:10 diluted solutions and undiluted solution (0.02 ml), together with a negative (saline) control. The sizes of areas of redness and wheals were measured at 15 min after the injection. A positive response was recorded when the mean wheal diameter was ≥ 9 mm or the mean area of redness was ≥ 20 mm. Following the intradermal tests, subcutaneous challenge tests were conducted. Undiluted local anesthetic (from 0.1 to 1.0 ml) was injected below the lateral surfaces of the patients' arms. The local findings observed around the injection site and the subjects' general symptoms and vital signs were examined after ≥ 30 min.

The majority of reactions occurred during dental procedures ($n = 47$), followed by minor surgical procedures ($n = 10$), mucosal

topical anesthesia ($n = 9$), intra-articular procedures ($n = 4$), nerve block anesthesia ($n = 1$), and spinal anesthesia ($n = 1$). Fifteen patients exhibited respiratory symptoms, such as dyspnea and bronchospasm, and the next most common reactions included general malaise ($n = 12$); gastrointestinal symptoms ($n = 11$), including nausea, vomiting, or diarrhea; urticaria ($n = 11$); facial erythema and edema ($n = 10$); tachycardia ($n = 10$); tremors ($n = 7$); shock ($n = 6$); syncope ($n = 6$); dizziness ($n = 6$); erythema and edema at the injection site ($n = 4$); sweating ($n = 4$); headache ($n = 3$); peripheral paresthesia ($n = 3$); weakness ($n = 3$); facial paleness ($n = 2$); visual obscuration ($n = 2$); fever ($n = 1$); and local pain at the injection site ($n = 1$).

As shown in Table 1, 4 patients (6.0%) displayed positive reactions, and 63 patients (94.0%) had negative reactions, indicating that most of patients had adverse reactions except allergic reactions after administration of local anesthetics. The patients in cases 1 and 2 exhibited positive reactions to multiple amide-type local anesthetics. They were subjected to tests (skin prick, intradermal, and subcutaneous challenge tests) of alternative agents, and no reactions were observed. The patient in case 3 displayed positive reactions to two esters and three amides. As no safe alternative agent was found for this patient, she has avoided local anesthetics ever since. The patient in case 4 only reacted to an amide agent in the subcutaneous challenge test, which led to the onset of urticaria. Because all four patients had positive reactions to local anesthetics without additives, it was thought that the patients had allergic reactions to local anesthetics agents themselves. Sixty-three patients demonstrated negative reactions to local anesthetics. One patient did not exhibit any reaction to amide-type local anesthetics without preservatives, but showed a positive reaction to methylparaben. Two patients developed dyspnea after testing with a placebo.

Ester-type local anesthetics used to cause immediate-type allergic reactions more frequently than other types of local anesthetics.¹ There have been sporadic reports of the immediate-type hypersensitivity to ester-type local anesthetics, while the delayed-type hypersensitivity to ester agents as demonstrated by a positive patch test is more commonly reported in the literature.¹ With regard to allergic reactions to amide-type local anesthetics, Fuzier *et al.* have reported among the 286 reports in which local anesthetics allergy was suspected, the immediate-type hypersensitivity to amide-type local anesthetics was found in three cases according to clinical features and skin tests,⁵ indicating that the immediate-type allergic reactions to amide-type local anesthetics are considered very rare. However, the frequency of allergic reactions to amide-type local anesthetics has recently increased probably because of the preferential use of these anesthetics.¹ In this study, 4 patients had allergic reactions to amide-type local

Peer review under responsibility of Japanese Society of Allergy.

<http://dx.doi.org/10.1016/j.alit.2017.07.003>1323–8930/Copyright © 2017, Japanese Society of Allergy. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Table 1
Details of the patients that exhibited positive test results.

Patient	Sex	Age	Type of procedure	Symptoms	Local anesthetic	Skin prick test	Intradermal test	Subcutaneous challenge test
1	F	61	Dental procedure	Tachycardia, nausea, dizziness	Lidocaine (amide)	Negative	Positive (1:1)	ND
					Dibucaine (amide)	Negative	Positive (1:1)	ND
					Bupivacaine (amide)	Negative	Positive (1:1)	ND
					Mepivacaine (amide)	Negative	Negative	ND
					Ropivacaine (amide)	Negative	Negative	Negative
					Procaine (ester)	Negative	Negative	ND
2	M	40	Mucosal topical anesthesia	Bronchospasm	Lidocaine (amide) [†]	Positive (1:1)	ND	ND
					Mepivacaine (amide)	Negative	Positive (1:10)	ND
					Procaine (ester)	Negative	Negative	Negative
3	F	82	Dental procedure	Facial erythema, facial edema, urticaria	Lidocaine (amide) [†]	Negative	Positive (1:1)	ND
					Mepivacaine (amide)	Positive (1:1000)	ND	ND
					Dibucaine (amide)	Positive (1:10)	ND	ND
					Procaine (ester)	Negative	Positive (1:10)	ND
					Tetracaine (ester)	Positive (1:100)	ND	ND
4	F	37	Dental procedure	Tachycardia	Lidocaine (amide)	Negative	Negative	Negative
					Mepivacaine (amide)	Negative	Negative	ND
					Propitocaine (amide)	Negative	Negative	Positive (Urticaria)

ND, not done.

[†] Local anesthetics that were causal for allergic symptoms. In cases 1 and 4, the causal local anesthetics that had been used before allergic symptoms were unknown.

anesthetics. Esters are metabolized to para-amino benzoic acid (PABA), which can cause immediate-type allergic reactions.⁴ Cross-reactivity has been detected between PABA and parabens, such as methylparaben and propylparaben, which are used as preservatives in local anesthetics, lotions, cosmetics, and food. In-group cross-reactions have been well characterized, but between-group cross-reactions, such as that seen in case 3, are extremely rare.²

Skin prick tests and intradermal tests are widely used to diagnose allergic reactions, but false-negative and false-positive reactions can occur. For example, esters and undiluted solutions tend to produce false-positive reactions.² It has been reported that the patients with positive skin prick tests to amide-type local anesthetics showed negative intradermal tests to them.⁶ Therefore, we should have examined intradermal tests using local anesthetics agents with positive prick tests in cases 2 and 3. The gold-standard diagnostic method for allergic reactions is a skin challenge test.⁶ Thus, it might be necessary to perform a subcutaneous challenge test (with the patient's informed consent and under careful observation) to avoid false-negative and false-positive reactions, even in cases involving positive skin test results. We did not perform subcutaneous challenge tests of local anesthetics with positive prick or intradermal tests in the patients (cases 1–3) because they had histories of systemic symptoms after administration local anesthetics (cases 1 and 2) or were at advanced age (case 3). Remarkably, among our patients, two exhibited dyspnea in response to the placebo. Bronchial and cardiovascular reactions are difficult to assess objectively; therefore, patients who experience such reactions should also be tested with a placebo.

In conclusion, immediate-type allergic reactions to local anesthesia are rare. However, some patients display immediate-type allergies to local anesthetics, including amide-type local anesthetics. Skin tests, including subcutaneous challenge tests, and if necessary, double-blinded controlled challenge tests with a placebo are important for confirming the presence of an allergy to local anesthetics or distinguishing between the effects of each anesthetic. Furthermore, if a patient exhibits an allergy to local

anesthetics, we recommend both avoidance of the relevant agents and that skin tests of unrelated agents should be performed with minimal kinds of agents in order to find safe alternatives and avoid the risk of further sensitization.

Conflict of interest

The authors have no conflict of interest to declare.

Naomi Nakamura ^a, Risa Tamagawa-Mineoka ^{*,a}, Koji Masuda, Norito Katoh

Department of Dermatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

* Corresponding author. Department of Dermatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan.
E-mail address: risat@koto.kpu-m.ac.jp (R. Tamagawa-Mineoka).

References

- Bhole MV, Manson AL, Seneviratne SL, Misbah SA. IgE-mediated allergy to local anaesthetics: separating fact from perception: a UK perspective. *Br J Anaesth* 2012;**108**:903–11.
- Thyssen JP, Menné T, Elberling J, Plaschke P, Johansen JD. Hypersensitivity to local anaesthetics—update and proposal of evaluation algorithm. *Contact Dermatitis* 2008;**59**:69–78.
- Becker DE, Reed KL. Local anesthetics: review of pharmacological considerations. *Anesth Prog* 2012;**59**:90–101.
- Finucane BT. Allergies to local anesthetics – the real truth. *Can J Anaesth* 2003;**50**:869–74.
- Fuzier R, Maryse LM, Mertes PM, Nicolas JF, Benoit Y, Didier A, et al. Immediate- and delayed-type allergic reactions to amide local anesthetics. *Pharmacoeidermiol Drug Saf* 2009;**18**:595–601.
- Kvisselgaard AD, Krøigaard M, Mosbech HF, Garvey LH. No cases of perioperative allergy to local anaesthetics in the Danish Anaesthesia Allergy Centre. *Acta Anaesthesiol Scand* 2017;**61**:149–55.

Received 1 April 2017

Received in revised form 4 June 2017

Accepted 27 June 2017

Available online xxx

^a These authors contributed equally to this study.