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Original Article

Atopic disease and/or atopy are risk factors for local anesthetic allergy in patients with history of hypersensitivity reactions to drugs?

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Abstract: Background and Objective: There is some concern among physicians that a positive history of adverse reactions to drugs and/or atopic disease remains a risk factor for developing a hypersensitivity reaction to local anesthetics (LA). In the present study we aimed allergy testing to LA is justified in patients with a positive history of hypersensitivity reactions to drugs additionally by atopy and atopic diseases. Patients and Methods: A standard questionnaire regarding demographic data, history of atopic disease (asthma, allergic rhinitis, atopic dermatitis, urticaria) was filled out, total IgE and eosinophil count were assesed for each patient. Skin prick tests (SPT), intradermal test (IDT) and subcutaneus incremental challenge test (ICT) were perfomed step by step with adrenaline free aritmal (lidokain HCL 2%, Osel) and citanest (prilokain HCL 2%, Astra Zeneca). Results: 239 patients with history of drug allergy were admitted. When we look at the results of skin tests and provocations with LA; while positive results of SPT werent found, 3 of IDT and 4 of ICT were positive. Of the all 4 patients that reacted to LA, had rhinosinusitis and a positive SPT reaction with aeroallergens, 1 had also food allergy, 2 had asthma. Conclusion: There is no increased risk requiring performing skin and provocation test for LA in the patients with a history of hypersensitivity reaction to drugs alone but additionally by presence of atopy, atopic disease and multidrug allergy history can increase the risk of LA allergy, the amount of evidence is scarce.

Keywords: Asthma, atopic, drug hypersensitivity, intradermal tests, lidocaine, local anesthetic, prilocaine, risk factors

Introduction

Local anesthetics (LA) are widely used before dental and minor surgical procedures. Most of the reactions are related to vagal, toxic, psychogenic reactions, pharmacological properties of the local anesthetics or the presence of subtances such as epinephrine, presevatives, parabens or metabisulfites [1, 2]. Even though hypersensitivity reactions are especially rare and account for less than 1% of all adverse reactions, uncertainty often remains regarding a possible allergic mechanism [3, 4]. This, later leads to a concern among physicians that a positive history of adverse reactions to drugs and/or atopic disease might be a risk factor for developing a hypersensitivity reaction to LA, and thus the patients are refering to allergy clinic for testing LA hypersensitivity.

For testing LA hypersensitivity; the skin prick test (SPT) and intradermal test (IDT) followed by subcutaneus incremental challenge test (ICT) in 15- to 20- min intervals are usually employed in protocols [5]. The ICT test plays an important diagnostic role especially for identifying non Ig-E mediated hypersensitivity reactions to LA which are occured frequently [6]. Although different centers prefer to skip SPT and IDT or only IDT in their allrgy testing protocol, these tests have limited value in the investigation of adverse reactions of LA because of their lack of reliable immunological identification of antigens and relatively high incidence of false positive reactions [7, 8]. We decided to use the full evaluation protocol; SPT, IDT and ICT as it more reliable.

In recent years, we have experienced an increase in the referral of patients to an allergy

clinic for finding a safe LA, in patients with a positive history of atopic disease and/or adverse reactions to drugs (especially nonsteroidal anti-inflammatory drugs; NSAİDs, antibiotics other than LAs). Our aim was to evaluate are these factors at an increased risk of developing allergic reactions to LA.

Materıals and methods

Patients

The study was conducted among patients admitted to our allergy clinic who gave a reliable history of urticaria/angioedema, nasoocular symptoms, bronchospasm after ingesting drugs; mostly NSAİDs, antibiotics, general anesthetics (GA), local anesthetics (LA) or others (may or may not have atopic diseases). A standard questionnaire regarding demographic data, history of atopic disease and drug adverse reactions was filled out, physical examination and blood analysis was made; total IgE and eosinophil count were assesed for each patient.

To asses the severity of airflow limitation and to confirm diagnosis of asthma, lung function and reversibility was measured in patients who have characteristic symptoms such as episodic breathlessness, wheezing, cough and chest tightness after excercise, exposure to airborne allergens or pollutants. In these patients if the degree of reversibility in FEV1 as 12% and 200 ml from the prebonchodilator value from basline, after inhalation of 400 ug salbutamol accompanied by airflow limitation, we confirmed the diagnosis of asthma [9].

Atopy was defined as a positive skin prick test (SPT) to at least one of the aeroallergens and nutritive allergens (SoluprickSQ, ALK-Abello' A/S, Hørsholm, Denmark) were used in SPTs: Positive histamine and negative (saline solution) controls were included. The puncture method with a 1 mm tip disposable lancet was used and a mean wheal diameter of 3 mm or greater than the control solution was considered positive.

Medications that could affect the results of the tests were withdrawn according to general guidelines [10]. None of the patients had episodes of urticaria or angioedema in the week stable for at least two weeks, and having an FEV1 70% over the predicted value. Patients who were pregnant or breast feeding, who had contraindications to eventual use of epinephrine and psychosomatic disorders were not included in the study. Informed consent was obtained from all patients and ethical approval from our Hospital Committee.

Protocol

Stepwise typing of safe LA included skin prick tests (SPT) and intradermal test (IDT) and subcutaneus incremental challenge test (ICT). Tests were performed with the following medications not including adrenaline: aritmal (lidocaine HCL 2%, Osel), citanest (prilocaine HCL 2%, AstraZeneca). The positive control was a prick test with histamine and the negative control with saline. The SPT was considered positive if a wheal of ≥3 mm than negative control. The next step involved IDT with LA diluted 1:100, but if severe reactions are suspected, 10-fold dilutions (starting at concentrations of 1:1000 or 1:10,000). It was assessed as positive if the size of initial wheal increased by 3 mm or more in diameter after 20 min. Skin tests were followed by subcutaneous challenge tests. The drug was injected in the lateral side of an arm 0.1 ml and 1 ml of undiluted drug in 30-min intervals [5]. During the procedure, blood pressure and FEV1 values, as well as the skin, ocular, nasal, and bronchial reactions, were monitored 30 min after the drug dose was injected. Patients were followed up to 24 hr to detect any delayed reaction. The challenge test was accepted as positive if one of the following symptoms existed: conjunctival reaction; upper and lower respiratory tract reactions such as sneezing, rhinorrhea, nasal blockage, dyspnea, wheezing, and cough with a 20% decrease in FEV1; cutaneous reactions such as local swelling, enduration and erythematous plaques around injection sites, erythema, pruritus with erythema, urticaria/angioedema.

If one of the steps yielded a reaction, the drug was excluded from further tests. In the case of an anaphylactic reaction, provocation was ceased and, after 24 h free from symptoms, another substance was tested.

Statistical analysis

Numerical results were expressed as mean ± standard deviation (SD). Nominal variables were expressed as percentage of the patients. A *p*

Table 1. Characteristic features of the patients

Sex (female/male); n (%)	176 (73.6)/63 (26.4)
Age (years); Mean (SD)	41.81 (13.77)
Baseline FEV1 (L); Mean (SD) (Median)	93.81 (21.15) (93.0)
Rate of positive skin prick test	
Aeroallergens	104 (43.5)
Nutritive allergens	15 (6.3)
Atopic diseases	
Asthma	80 (33.5)
A.Rhinitis	39 (16.3)
Urticaria	24 (10.0)
A.Dermatitis	2 (0.8)
Implicated drugs, n (%)	
NSAIDs	168 (70.3)
Antibiotics	129 (54.0)
NSAID+Antibiotic	75 (31.4)
Local anesthetic	11 (4.6)
General anesthetic	9 (3.8)
Total IGE; Mean (SD) (Median)	193.16 (396.11) (78)
Eosinophil; Mean (SD) (Median)	2.88 (2.30) (2.40)

value of less than 0.05 was considered significant. The Statistical Package for Social Sciences (SPSS) for Windows version 14.0 (Chicago, IL, USA) was used to analyze the data.

Results

239 patients (63 men, 176 women) were admitted to our allergy clinic with reiable history of drug ractions; According to patient histories, the majority of intolerance reactions were due to NSAIDs. Only 11 (4.6%) of them had a documented history of adverse events after administration of LA, including 3 after lidocaine, 1 after mepivacaine, and 4 after articaine. In the remaining cases, names of the drug administered werent known. In this group, patients reported the following symptoms: loss of consciousness (n = 1), shortness of breath (n = 7), urticaria/angioedema (n = 6), nausea-vomiting (n = 2), near fainting (n = 4), and palpitations (n = 3).

Among these patients, 80 patients (33.5%) exhibited clinical evidence of asthma (54 previously diagnosed, 26 newly diagnosed), 39 patients (16.3%) had rhinosinusitis, 2 patients (0.8%) had atopic dermatitis and 24 were suffering from chronic urticaria (10%).

SPT analysis was performed on all subjects. In 11 cases, prick tests were not reliable due to dermatographism, and atopy ratio was 43.5% (n = 104) in the study group.

Although patients mean eosinofil count was in normal limit, mean total IgE level is higher (193.16 IU/ml) in our study group. Patients demoghraphic characteristics and evaluated risk factors are given in **Table 1**.

When we look at the results of skin tests and provocations with LA; positive results of SPT werent found, of IDT in 3 cases were positive. 2 patients IDT tests were positive with lidocaine, 1 patient with prilocain. During the ICT, 1 patient reported atypical symptoms (near, fainting, elevated blood pressure and dizziness) that reappeared also after placebo administration. 4 of ICT were assessed as positive; 1 patient with lidocaine and prilocain (but IDTs were negative), 1 patient with prilocaine, 2 patients with lidocaine (IDTs were also positive). The symptoms were enduration and erythematous plaques around injection sites, skin redness, shortness of breath, near fainting and urticaria. Of the all 4 patients that reacted to LA, had rhinosinusitis and a positive SPT reaction with aeroallergens, 1 patient had also food allergy. Although eosinofil counts were normal, 2 patient had asthma and high level of total Ig E. There is no patient suffering from chronic urticaria and atopic dermatitis in these LA intolerant group. Detailed information about these reactive patients are given in **Table 2** and analyzed risk factors of LA allergy are given in **Table 3**.

Although we observed no significant difference between two groups regarding prevalence of risk factors and this condition results from small group of patients determined to have allergy to local anesthetics; we can say that risk of allergy to local anesthetics in the patients with a history of drug hypersensitivity reactions may be increased additionally by atopic diseases, history of a. rhinosinusitis, presence of hypersensitivity to aeroallergens and history of multidrug allergy even though not significantly (**Table 4**).

Discussion

There is some concern among physicians that a positive history of atopic disease and/or adverse reactions to drugs remains a risk fac-

Table 2. Detailed information reacted to LA

Patient No	Age/Sex	History of drug reaction	Atopic Disorder	Atopy	IDT with		ICT with	
					Lidocaine	Prilocaine	Lidocaine	Prilocaine
1	47/F	NSAID Antibiotic	Asthma A.rhinitis	Mite	Negative	Negative	Positive	Positive
2	28/M	NSAİD Antibiotic	Asthma A.rhinitis	Mite Pollen Food	Negative	Positive	Negative	Positive
3	32/F	NSAID Antibiotic Mepivacaine	A.rhinitis	Mite	Positive	Negative	Positive	Negative
4	48/F	NSAID Acetylsalicylic acid	A.rhinitis	Mite Pollen Aspergillus	Positive	Negative	Positive	Negative

Table 3. Risk factors of LA allergy

	Allergy to LA Tested		[a]P
	Positive	Negative	
	n (%)		
N	4	235	
Sex (m:f)	1:3	62:173	0.000
Implicated drugs			
NSAI	4(100.0)	164 (69.8)	0.321
Antibiotic	3 (75.0)	126 (53.6)	0.627
NSAI+Antibiotic	3 (75.0)	72 (30.6)	0.093
Local Anesthetic	1 (25.0)	10 (4.3)	0.173
General Anesthetic	0 (0.0)	9 (3.8)	0.000
Rate of positive skin prick test			
Aeroallergens	4 (100.0)	100 (42.6)	0.035*
Nutritive allergens	1 (25.0)	14 (6.0)	0.230
Atopic diseases	3 (75.0)	99 (42.1)	0.315
Asthma	2 (50.0)	78 (33.2)	0.603
A.Rhinitis	4 (100.0)	36 (15.3)	0.001**
Urticaria	0 (0.0)	24 (10.2)	0.000
A.Dermatitis	0 (0.0)	2 (0.9)	0.000
	Mean (SD) (Median)		[b]P
Age	38.75 (10.24) (39.5)	41.86 (13.84) (41.0)	0.680
Total IGE	350.03 (574.10) (77.0)	189.96 (393.11) (78.0)	0.786
Eosinophil	2.43 (0.96) (2.45)	2.89 (2.32) (2.40)	0.536

[a]Fisher's exact test; [b]Mann Whitney U test; **P<0.01.

tor for developing a hypersensitivity reaction to LA. In the present study we observed allergy testing to LA is not justified in patients with a positive history of hypersensitivity reactions to drugs alone, but additionally by atopic disease and atopy it can be justified.

In our study, SPT with epinefrin free LA ((lidokain HCL 2%, Osel, prilokain HCL 2%, AstraZeneca) werent positive, positivity was determined at quite low rates in IDT (1.2%) and ICT (1.6%) consistent with the study performed by Troise et al. [14] including 386 patients. According to patient histories the majority of hypersensitivity reactions were due to NSAIDs. 4 patient developing a hypersensitivity reaction to LA had a history of adverse reactions to more than one NSAID and 3 patient had an additional history of adverse reactions to antibiotics. History of LA hypersensitivity reaction were seen in only 11 patients. In this group, only one patient reacted to lidocaine who had a history of mepivacaine allergy. But we can not say that history of adverse reactions to LA increase or not increase the odds of being test-positive because of inadequate number of patients with history of LA intolerance. However, in a study performed in 141 patients with a history of allergy to local anesthetics, it was confirmed that these were

Table 4. Odds Ratio for Positive Test by Risk Factors

		Odds Ratio (95% CI)	P
Atopy		-	0.996
History of	NSAI allergy	-	0.997
	Antibiotic allergy	2.595 (0.266-25.313)	0.412
	NSAI+Antibiotic allergy	6.792 (0.695-66.407)	0.096
	LA-GA allergy	4.019 (0.397-40.633)	0.219
Asthma		2.013 (0.278-14.559)	0.488
Urticaria		-	0.998
A.Rhinitis		-	0.995
High level IGE		1.253 (0.173-9.075)	0.823
Eosinophilia		-	1.000

not allergic reactions with intradermal tests or intra-oral challenge tests. Again it was determined that these reactions were psychogenic and a few of them was due to intravascular administration [15]. In another study conducted by Victorija Erdelcic et al. [16] reported the odds were not significantly raised since cross reaction between different amide anesthetics is not expected. These results are consistent with the study by Gall et al. [17] who did not find any positive skin tests in a group of 177 patients with a history of adverse reactions to LA. But in our study 1 patient had reacted with both lidocaine and prilocaine in ICT although they are different amides. On the other hand, the proportion of false positive skin tests is reported to be 10-36% by Wasserfallen et al. [18]. Since false positivity can be seen in intradermal test at 1/10 dilution, we preferred a 1/100 dilution and we did not remain limited to skin test alone and we complete the protocol with ICT which was gold standard for diagnosis.

Percentage of atopy, in a study performed in Turkey, determined in the population with a risk of atopy was similar to our results (43.5% vs. 37.7%, P>0.05) [12]. But, when we compared it with the atopy rate in the general population, our atopy rate was found to be significantly higher (43.5% vs. 25%, P<0.05) [13]. Mite allergens were the most common cause of allergy with a ratio of 36.8% (n=88). In a study performed in 2067 patients, the patients with and without history of drug-induced hypersensitivity reactions were compared regarding atopy, it was determined that the rates were similar [19]. But in our study atopy rate is higher than our population and we can suggest that atopy can be a risk factor for LA hypersensitivity in patients with history of hypersensitivity to drugs, due to determination of atopy in all of these LA intolerant patients.

When we look at atopic disease prevalence in our study; asthma was higher (33.5% vs 7.1-9%, P<0.01), atopic dermatitis was lower (0.8% vs 8.2-9.6%, P<0.01) but there was no difference in rhinosinusitis (16.3% vs 14-18.7%, P>0.05), than our population of man and woman [11]. When the patients included in our study were evaluated with careful history, physical examination and reversibility testing for pulmonary function; it was observed that there were many patients (22.5%) with previous diagnosis of asthma, irregular use of bronchodilator and/or inhaler steroids or treated for long-term or new diagnosis of asthma (10.8%). Apart from the other studies, determination of higher prevalence of asthma in our patients can be associated with detailed history and spirometric measurements with reversibility testing. While prevalence of asthma, allergic rhinitis and atopic dermatitis were determined to be higher in a study [19], in our study history of allergic rhinitis and chronic urticaria was similar but asthma higher from the normal population and atopic dermatitis was present in a few patients. In the patients with local anesthetic hypersensitivity (n=4), while allergic rhinitis and asthma was present at a rate of 100% (n=4) and 50% (n=2), respectively, chronic urticaria and atopic dermatitis were not observed.

While mean total IGE value and level of peripheral blood eosinophil of the patients with local anesthetic hypersensitivity were within normal ranges in the study performed by Victorija Erdelcic et al. [16] in our study mean total IGE value of the LA intolerant patients was higher but the level of peripheral blood eosinophil count was within normal ranges.

Conclusıon

In the patients with a history of drug hypersensitivity reactions, asthma prevalence, atopy rate and mean total IgE levels are higher. We can say that the history of drug allergy apart from atopic disease does not increase the risk

for allergy to local anesthetics. Therefore, there is no increased risk requiring performing skin and provocation test for local anesthesia in the patients with a history of hypersensitivity reaction to drugs alone. However; additionally by presence of atopy, atopic disease and multi-drug allergy history can increase the risk of LA allergy, the amount of evidence is scarce. Large scale studies are needed to determine the risk factors for indications of referral of the patients to immunology and allergy clinics for testing LA hypersensitivity. Lidocaine and prilocaine not containing epinephrine are safe in the patients referring for testing LA hypersensitivity and they can be preferred as the first choice.

Disclosure of conflict of interest

None.

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