

Effect of premedication on side effect frequency in patients to whom immunotherapy is applied

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Abstract

Aim: In this study we aimed to investigate whether there are differences in terms of the frequency and severity of side effects in patients to whom premedication were given/or not before the application of subcutaneous allergen specific immunotherapy.

Material and method: Patients receiving subcutaneous allergen-specific immunotherapy in our clinic between October 2014 and October 2015 were evaluated for side effects. In patients to whom subcutaneous allergen-specific immunotherapy was applied and reaction was occurred against this therapy; allergen type, reaction intensity and duration, and also use of premedication were recorded. When the patients were assessed in terms of side effects; edema and/or erythema from 2 to 5 cm, which were beginning within the first 24 hours in the injection site. That was defined as 'local reaction' and edema and/or erythema, if it was greater than 5 cm defined as 'broad local reaction'.

Results: Total of 101 patients, to whom allergen specific immunotherapy was applied, were included. In a year of the study; total of 660 injections were applied to 101 patients and reaction to injections were observed in 31 injections (4.6%). Reaction was observed in 20 individuals (19.8%). No significant difference was found between premedicated and non-premedicated groups in terms of the percentage of side effects and risk of side effects ($p > 0.59$).

Conclusion: In our study; patients with or without premedication were compared in terms of side effect frequency. In premedication group; ratio of local reaction was found to be low (20%). It was thought that premedication could reduce local reactions but did not prevent extensive local reaction. There was no difference when comparing the side effect frequency between the two groups.

Keywords: Premedication; Immunotherapy; Side Effect.

INTRODUCTION

Allergen specific immunotherapy (AIT) is the only treatment option that can alter the natural course of allergic diseases (1). The treatment of allergic rhinitis and allergic asthma include patient education, allergen prevention, and drug treatment and AIT where appropriate (2). Subcutaneous AIT application, starting from low doses is necessary in order to ensure that the patient can tolerate the same allergen again (1,3,4).

During subcutaneous AIT applications, various local reactions and, rarely, systemic reactions which can cause death, can be seen (3,4,6,7). Indications and expected benefits and risks should be considered together in the selection of patients for subcutaneous AIT (8). The major risk of subcutaneous AIT is anaphylaxis (8-10). The fact that the patient is asthmatic is an important risk factor for systemic reactions (5). However, in severe asthmatic cases, the AIT is considered to be contraindicated because

of the risk of serious systemic reactions (5,8). Reactions such as itching, redness and swelling that occur at the injection site in patients who have been treated with subcutaneous AIT are called local reactions. However, it is known that local reactions do not predict the future systemic reactions and are well tolerated in many patients. It has been reported that the common local reactions in some patients exceeding 10 cm and lasting for more than 24 hours can be risk factors for future systemic reactions (7,8).

In this study we aimed to investigate whether there are differences in terms of the frequency and severity of side effects in patients to whom premedication was given/or not before application of subcutaneous allergen specific immunotherapy.

MATERIAL and METHODS

Patients to whom subcutaneous AIT was applied in our clinic between October 2014 and October 2015 were

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evaluated for side effects. Ethics committee approval was obtained from Cukurova University (decision no. 62/14). Form was filled and information about the study was given. Written and verbal consents were obtained from patients. In patients to whom subcutaneous allergen-specific immunotherapy was applied and reaction was occurred against this therapy; allergen type, reaction intensity and duration, use of premedication were recorded. For premedication; cetirizine hydrochloride (5mg/day), second generation H1 antihistamine, was used orally one hour prior to subcutaneous AIT. All patients were prescribed the same second-generation antihistamines. Because of the retrospective nature of the study, the patients were not previously divided into groups. All the patients to whom immunotherapy was applied in our clinic were asked whether they had premedication in every application and were observed for one hour in terms of side effects. After injections, the same clinician checked up the patients. Vaccines, which were purchased from ALK drug and Allergo drug companies, were used. In multiple immunotherapy; vaccines were taken from two or three separate bottles and were injected to right and left arms separately. In patients receiving triple immunotherapy, every injection was administered on a different day. When the patients were assessed in terms of side effects; edema and / or erythema from 2 to 5 cm, beginning within the first 24 hours in the injection site was defined as 'local reaction' and edema and /or erythema greater than 5 cm was defined as 'broad local reaction'. Systemic reactions were evaluated according to subcutaneous immunotherapy systemic reaction classification system of World Allergy Organization (grade 1-5). Conjunctival or cutaneous or upper respiratory symptoms were evaluated as grade 1, lower respiratory tract or gastrointestinal symptoms as grade two, lower respiratory and laryngeal edema without stridor as grade three, hypotension without upper and lower respiratory insufficiency or loss of consciousness as grade four and death was evaluated as grade five (11).

Statistical analysis

All data were analyzed with the Statistical Package for the Social Sciences version (SPSS Inc; Chicago, IL, USA). In the analysis of the data, frequency (%), mean, standard deviation, minimum, maximum values were used for descriptive statistics and chi-square test was used for comparison of groups. Statistical significance was accepted as $p < 0.05$.

RESULTS

One hundred and one patients, to whom subcutaneous AIT was applied, were included in the study. Sixty of the patients were males (65.3%), 35 were females (34.7%). The mean age was 11.5 ± 2.4 (min: 6 max: 18) years. In study group; 47 patients were taking subcutaneous AIT for mite (46,5%), 12 patients for mite + fungus (11,9%), twelve patients for pollen (11,9%), nine patients for mite+ pollen (8,9%), seven patients for fungus (6,9%), six patients for fungus + pollen (5,9%), one patient for mite+ pollen+ fungus (1,0%) and seven patients for bee venom

(6,9%) (Table 1). The reaction rate was highest after AIT application for mite + fungus + pollen and the reaction rate was 44.4%. (Table 1).

Table 1. Distribution and reaction rates of patients receiving subcutaneous AIT

	Patient distribution (n:101)	Reaction ratio
Mite	47 (46.5%)	8 (17%)
Mite + Fungus	12 (11.9%)	0
Pollen	12 (11.9%)	2 (16.6%)
Mite+ Pollen	9 (8.9%)	4 (44.4%)
Fungus	7 (6.9%)	3 (42.8%)
Fungus + Pollen	6 (5.9%)	2 (33.3%)
Mite+Fungus+Pollen	1 (1.0%)	1 (100%)
Bee Venom	7 (6.9%)	0

During the study period, total 660 injections were applied to 101 patients and among these; reaction was observed in 31 injections (4,6%). Reaction was observed in 20 patients (19,8%). It was also observed that the reaction was repeated with dose reduction in 11 of the 20 patients who had a reaction and total 31 reactions were observed. Seventy five of the 101 patients received premedication (74.3%) and 26 (25.7%) did not receive premedication. Reaction was occurred in 15/75 patients who received premedication (20,0%). Reaction was occurred in 5/26 patients who did not receive premedication (19,2%). There was no difference in terms of reaction between premedicated and non-premedicated groups ($p > 0,59$) (Table 2).

Table 2. Reaction rates in pre-,medicated and non-pre-medicated patients

	Number of patients	Reaction (+)	Ratio	p value
Premedicated group	75	15	20.0	$p > 0.59$
Non-premedicated group	26	5	19.2	$p > 0.59$

In the group receiving premedication; local reaction was seen in 3 patients (20%) and extensive local reaction was seen in 12 patients (80%) among total 15 patients in whom reaction was occurred. The same reaction was repeated with dose reduction in eight of 15 patients (six large local reactions, two local reactions). A total of 5 local and 18 extensive local reactions were observed in the group without premedication. In patients without premedication, the same reaction was repeated in three patients following dose reduction. A total of 8 local reactions were observed in the group without premedication.

In one patient to whom AIT was applied for mite + pollen; extensive local reaction (20 cm edema and erythema at the injection site) was occurred and grade 1 systemic reaction (rhinitis and conjunctivitis) was occurred with AIT application for pollen. One (0.15%) systemic reaction was observed in 660 injections (Table 3).

Table 3. The distribution of reaction types in premedicated and non premedicated patients

Pre-medication	Local reaction number of patients	Extensive local reaction Number of patients	systemic
Applied	3 (20%)	12 (80%)	1
Not applied	5 (100%)	0	0

Of the 20 patients who developed the reaction, 15 were males (75%), five were females (25%). Of the 20 patients who developed the reaction, 15 were in the maintenance period, 5 were in the onset period. Five patients were followed-up with the diagnosis of allergic asthma (25%), 13 patients with allergic rhinitis + asthma (65%) and two patients with rhinitis (10%). Among patients with reaction; eight patients received AIT because of mite (40%), four patients because of mite + pollen (20%), three patients because of fungus (15%), two patients because of pollen (10%), two patients because of fungus + pollen (15%) and one patient because of mite + pollen+ fungus (5%).

Seventy three patients were receiving single (72.3%), 27 patients were receiving double (26.7%) and one patient was receiving triple allergen AIT. Among patients in whom reaction was occurred; 13 received single (65%) and 7 received multiple (six had double and one had triple) (35%) AIT. There was no significant difference in the incidence of side effects between single and multiple AITs ($p=0.416$). However, it was seen that multiple AIT administration increased the risk of developing side effects by 1.53 (0.54-4.37) times compared to single AIT application (Table 4).

Of the 35 female patients in the study group, 9 (17.1%) were not receiving premedication whereas 17 male patients among total number of 66 (19.3%) male patients were not receiving premedication. We encountered not receiving premedication more often in male patients (Table 5).

Table 4. Reaction ratios in single allergen and multiple allergen immunotherapy

AIT	Number of patients	Number of Patients with reaction
Single	73	13 (17.8%)
Multiple	28	7 (25%)

Table 5. Gender distribution in premedicated and non-premedicated patients

Gender	Receiving premedication	Not receiving premedication	Total
Female	26 (82.9%)	9 (17.1%)	35 (34.7%)
Male	49 (69.7%)	17 (30.3%)	66 (65.3%)

DISCUSSION

Subcutaneous AIT initiation decision should be given by evaluating indications and risks together by the clinician for each patient and immunotherapy protocol should be determined. Various local and systemic side effects may

occur during AIT applications. All patients in our study were treated with the classic protocol. It is known that there is a higher rate of systemic reaction in the rush (cluster) AIT protocols compared to the classic AIT protocol (5,6,8).

Although premedication is not routinely recommended during subcutaneous AIT, it has been shown to reduce local and systemic reactions in rush, cluster, classical protocols (7). In the literature, it was stated that asthma cases has a higher risk of severe systemic reaction than those with allergic rhinitis only (6,9,11,12). In our study, 65% of the patients who developed reaction were found to have allergic asthma + rhinitis and 25% of the patients were found to have allergic asthma. Only those with allergic rhinitis had a reaction rate of 10%. It is known that the most risky period in terms of side effects is the period in which the dose is increased (5). In one study, the risk of systemic reaction was found to be 3.3% for meadow pollen and 0.7% for birch tree pollen (13). In another study, 423 cases had a systemic reaction in 0.3% of the total number of injections. Estimated risk for fatal reaction is one in 2.5 million injections (7). In a study covering the past 15 years, the systemic rate of reaction per injection was found to be 0.2% in classical AIT (9,11). In Rush IT these rates are up to 30% (7,8). In our study, one (0.15%) grade 1 systemic reaction was observed in 660 injections and this was found to be compatible with the literature. Following subcutaneous allergen-specific immunotherapy applications, local reactions occur with certain ratios and are not life-threatening. Local reaction frequency was found in 26-82% of patients in two studies, which were reported in 0.7-4% of injections (14,15). In our study, reaction was observed in 19.8% of patients. Reaction was seen in 4.6% of all injections, consistent with the literature. In a study conducted in the pediatric population; ratio of local reactions was 3% and large local reactions was 0.16% according to the number of injections. In this study, local reactions of IT were reported to be more frequent in maintenance doses compared to the dose escalation phase (16). In our study, 75% of the patients with similar reactions were in the maintenance period. There is general consensus that local reactions during subcutaneous AIT do not increase the risk of a systemic reaction in subsequent injections (6). In a retrospective study; it was seen that large local reactions (greater than 8-10 cm or larger than hand mass) increased the risk of systemic reactions (17). In our study, one patient with a systemic reaction had a 20 cm extensive local reaction. In our study, local reactions were seen in 13 of 660 injections (1.9%) and extensive local reactions were seen in 18 injections (2.7%). We think that local reaction rate is low because 75 patients (74.2%) received premedication in our study. In our study, 75% of patients with similar reactions were in the maintenance period. A total of 31 reactions were observed in 20 patients with a reaction. It was seen that some of these reactions were repeated again in the next dose or at the reduced dose. In our study; premedication and non-premedication patients were compared in terms of frequency of side effects. Of the 75 patients receiving

premedication, 15 (20.0%) had a reaction, 12 (80%) had an extensive local reaction. Local reaction rate was low in premedicated group (20%). Premedication was thought to reduce local reactions but did not prevent large local reactions. The only patient with a systemic reaction was in the premedicated group. Five of the 26 patients who did not receive premedication (19.2%) had reaction and all of these reactions were local reactions. No extensive local reactions were found in the group without premedication.

In our study; local reaction ratio in premedicated group was 3,9% (3 of the 75 patients had local and 12 had extensive local reactions) and local reaction ratio in non-premedicated group was 19.2%, the local reaction was found to be significantly lower in premedicated group than those who did not receive premedication. The most commonly used allergen in our work was house dust mite (46,5%). Among the ones applied as single and double AIT; the highest rate of reaction was found in mite + pollen group (44.4%). No reaction was observed with bee venom, it was thought that there was no reaction due to the fact that only single immunotherapy was performed in patients who received bee venom immunotherapy and all of these patients were receiving premedication according to the records.

Reaction rate was 17.8% in patients receiving mono-AIT, compared with 25% in patients receiving multiple AITs. No significant difference was found between single and multiple RT in terms of reaction ($p=0,416$). However, it was seen that multiple AIT administration increased the risk of developing side effects by 1.53 (0.54-4.37) times comparing to single AIT.

Of the 35 female patients in the study group, 9 (17.1%) were not receiving premedication whereas 17 male patients among total number of 66 (19.3%) male patients were not receiving premedication. We found that not receiving premedication was more often in male patients.

The limitation of our study according to us, it is asking to patients whether they had premedication or not previously. Although we thought that we got the right answer; patients receiving premedication before the administration of could receive antihistamines in the clinic.

As a result of this study; we observed that premedication did not decrease extensive local reactions and systemic reactions but decreased the frequency of local reaction and reaction ratio was increased in mite + pollen group and risk of reaction increased with multiple AIT.

Treatment of local reactions with oral, topical antihistaminic preparations and local ice application is usually sufficient. In cases of extensive local reactions; lesions regress within 2-5 days with the use of antihistaminic and analgesic drugs. It is known that the most severe systemic reactions occur within the first 30 minutes after injection. Depending on the severity of the systemic reaction; an appropriate treatment approach will be necessary. For this reason, patients should be kept in

the clinic for at least half an hour.

Due to the risk of systemic reactions, it is recommended that injections of AIT should never be administered at home (3).

As a result, local, extensive local and systemic reactions can be seen in AIT with a remarkable ratio. There was no significant difference in reaction frequency between premedicated and non-premedicated groups, but local reactions were found to be less in premedicated group. Although there are concerns that premedication with antihistamines may mask some signs and symptoms of the systemic reaction before immunotherapy injections; it has been reported that this application reduces the frequency of systemic reactions and thus facilitates attainment of target maintenance dose (8).

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