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Adverse Reactions to Allergen Injection : The Siriraj Experience

Chaweewan Bunnag, M.D.*
Perapun Jareoncharsri, M.D.*
Prayuth Tunsuriyawong, M.D.*
Paraya Assanasen, M.D.*
Siriporn Voraprayoon, B.Ed.*
Phadej Dachpunpour, B.Sc.*
Chaiporn Manochnond, Dip.Med.Sc.Tech.**
Bangon Pinkeaw, M.Sc.*

Abstract : **A retrospective review of the medical records of adult patients, who had skin testing and allergen immunotherapy at the ENT Allergy Clinic, from January 1987 to December 1999 was performed, to ascertain the incidence of adverse reactions to allergen injection. For skin prick testing, 5,879 patients with 82,306 skin tests were recorded with no adverse systemic reactions. For intradermal testing, 5,490 patients with approximately 109,800 tests were recorded and two patients developed mild systemic reactions which were probably related to the test. The systemic reaction rate of intradermal skin testing was therefore 36.4 per 100,000 patients or 2.2 systemic reactions per 100,000 intradermal tests. The overall reaction rate of both types of allergy skin test in 11,369 patients tested for aeroallergens was 0.018% or 17.6 systemic reactions per 100,000 patients. Concerning immunotherapy, 42,810 allergen injections were recorded, the rate of excessive local reactions was 4.8% (4.08% were immediate and 0.77% were delayed types), and the rate of systemic allergic reactions was 0.08%. None of the reactions was fatal.**

In a prospective study conducted from January 2000 to December 2001, 4,764 allergen injections were performed with 27 systemic reactions occurring in 23 patients (7 men and 16 women). Twenty-two events were classified as mild to moderate (0.46%) and 5 events were acute severe reactions (0.11%). No cases of hypotension or laryngeal edema were observed and none of the reactions was fatal.

**Department of Otolaryngology, **Department of Pharmacology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700.*

The possible risk factors for developing a systemic reaction during immunotherapy in this study were : vaccines comprising grass/weed pollen or house-dust mite, an increased dose, symptomatic asthmatics, prior systemic reactions and changing to a new vial. The incidence of adverse reaction after allergen injection and the possible causative factors associated with immunotherapy in our clinic are similar to other reports from western countries. In order to minimize the number and the severity of systemic reaction, an allergen injection should be performed by physicians and personnel who are well aware of the risks and well trained to recognize and manage the systemic reactions immediately.

Key words : allergen injection, skin prick test, intradermal test, immunotherapy

เรื่องย่อ : **ปฏิกิริยาไม่พึงประสงค์ที่เกิดจากการฉีดสารก่อภูมิแพ้ : ประสบการณ์ในโรงพยาบาลศิริราช**

ฉวีวรรณ บุนนาค พ.บ.*, พีรพันธ์ เจริญชาศรี พ.บ.*, ประยุทธ ตันสุริยวงษ์ พ.บ.*, ปารยะ อาศนะเสน พ.บ.*, ศิริพร วรประยูร ค.บ.*, เผด็จ เดชพันพัว วท.บ.*, ชัยพร มโนชนนท์ ป.วิทยาศาสตร์การแพทย์, บังอร ปิ่นแก้ว วท.ม.***

**ภาควิชาโสต นาสิก ลาริงซ์วิทยา, **ภาควิชาเภสัชวิทยา, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพมหานคร 10700.*

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การศึกษาแบบย้อนหลังในผู้ป่วยที่มารับการทดสอบภูมิแพ้ทางผิวหนังและการฉีดวัคซีนเพื่อรักษาโรคภูมิแพ้ที่คลินิกโรคภูมิแพ้ทางหู คอ จมูก โรงพยาบาลศิริราช ระหว่างเดือนมกราคม พ.ศ. 2530 ถึงเดือนธันวาคม พ.ศ. 2542 มีผู้ป่วยมารับการทดสอบภูมิแพ้โดยวิธีสะกิด จำนวน 5,879 ราย คิดเป็น 82,306 ครั้ง โดยไม่พบมีปฏิกิริยาไม่พึงประสงค์เกิดขึ้นเลย สำหรับการทดสอบภูมิแพ้โดยวิธีฉีดเข้าในผิวหนังได้ทำในผู้ป่วยจำนวน 5,490 ราย คิดเป็นประมาณ 109,800 ครั้ง พบมีปฏิกิริยาทั่วร่างกายเล็กน้อยในผู้ป่วย 2 ราย ที่อาจเกิดเนื่องจากการทดสอบภูมิแพ้ คิดเป็นอัตราการเกิดปฏิกิริยาทั่วร่างกายเนื่องจากการทดสอบภูมิแพ้โดยวิธีฉีดเข้าในผิวหนัง 36.4 ครั้งต่อจำนวนผู้ป่วย 100,000 ราย หรือคิดเป็น 2.2 ครั้งต่อการฉีดทดสอบ 100,000 ครั้ง อัตราการเกิดปฏิกิริยาโดยรวมของการทดสอบภูมิแพ้ทั้งสองวิธีในผู้ป่วยจำนวน 11,369 รายที่ได้ทดสอบกับสารก่อภูมิแพ้ชนิดที่มีอยู่ในอากาศเป็นร้อยละ 0.018 หรือ 17.6 ครั้งต่อผู้ป่วย 100,000 ราย สำหรับการฉีดวัคซีนเพื่อรักษาโรคภูมิแพ้ ในช่วงเวลาดังกล่าว ซึ่งมีการฉีด 42,810 ครั้ง อัตราการเกิดปฏิกิริยาเฉพาะที่ที่มากเกินกำหนดเป็นร้อยละ 4.8 โดยร้อยละ 4.06 เป็นชนิดเกิดขึ้นทันทีหลังฉีด และร้อยละ 0.77 เป็นชนิดที่เกิดหลังจากฉีดเป็นเวลานาน อัตราการเกิดปฏิกิริยาภูมิแพ้ทั่วร่างกายเป็นร้อยละ 0.08 ไม่มีรายงานการเกิดปฏิกิริยาที่รุนแรงถึงขั้นผู้ป่วยถึงแก่กรรม

จากการศึกษาแบบไปข้างหน้า ในผู้ป่วยที่มารับการฉีดวัคซีนเพื่อรักษาโรคภูมิแพ้ระหว่างเดือนมกราคม พ.ศ. 2543 ถึงเดือนธันวาคม พ.ศ. 2544 มีการฉีดวัคซีน 4,764 ครั้ง และมีการเกิดปฏิกิริยาภูมิแพ้ทั่วร่างกาย 27 ครั้ง ในผู้ป่วยจำนวน 23 คน (เป็นชาย 7 คน และหญิง 16 คน) ปฏิกิริยาที่เกิด 22 ครั้ง เป็นชนิดอาการเล็กน้อยถึงปานกลาง (ร้อยละ 0.46) และ 5 ครั้ง เป็นปฏิกิริยาชนิดรุนแรง (ร้อยละ 0.11) แต่ไม่มีผู้ที่ความดันโลหิตตกมากหรือกล่องเสียงบวม และไม่มีผู้ใดถึงแก่กรรมเนื่องจากปฏิกิริยาจากการฉีดวัคซีน ปัจจัยเสี่ยงที่ทำให้เกิดปฏิกิริยาไม่พึงประสงค์ชนิดทั่วร่างกายที่คาดว่าเกิดจากการฉีดวัคซีนในการศึกษาครั้งนี้ ได้แก่ ส่วนประกอบของวัคซีนที่เป็นละออง

เกสรหญ้า/วัชพืช หรือไรฝุ่น, การเพิ่มขนาดของวัคซีนที่ฉีด, ผู้ป่วยโรคหืดที่กำลังมีอาการหอบ, ผู้ที่เคยมีปฏิกิริยาไม่พึงประสงค์ที่เป็นชนิดทั่วร่างกายมาก่อน และขณะเปลี่ยนวัคซีนขวดใหม่ อุบัติการณ์ของการเกิดปฏิกิริยาไม่พึงประสงค์ตามหลังการฉีดสารก่อภูมิแพ้และปัจจัยที่น่าจะเป็นสาเหตุที่พบในรายงานนี้คล้ายกับที่มีรายงานจากประเทศซีกโลกตะวันตก การที่จะลดอุบัติการณ์และความรุนแรงของปฏิกิริยาไม่พึงประสงค์ที่อาจเกิดจากการฉีดสารก่อภูมิแพ้ แพทย์และบุคลากรที่เกี่ยวข้องต้องได้รับการฝึกอบรมมาทางด้านนี้โดยเฉพาะ เพื่อให้ทราบปัจจัยเสี่ยงจะได้หาทางป้องกัน และเพื่อสามารถให้การวินิจฉัยและรักษาปฏิกิริยาไม่พึงประสงค์ที่เกิดขึ้นได้อย่างทันท่วงที

INTRODUCTION

Allergen injection includes both skin testing and immunotherapy. Allergen injections have been introduced over one hundred years ago and are considered safe but systemic allergic reactions and fatalities have occasionally been reported. These are of great concern to practicing allergists. In particular, during the last two decades, there have been several surveys concerning the incidence of fatalities after specific allergen immunotherapy. For example, data collected in the United Kingdom by the Committee on Safety of Medicines included 26 deaths after injection of allergenic extracts between 1957 and 1986, 5 of which occurred during the preceding 18 months[1]. In Germany, Siefert[2] reported that between 1981 and 1988, there were 22 deaths as a result of allergen immunotherapy.

In the United States, Reid et al[3] collected data between 1987 and 1991, and found 19 deaths following allergen immunotherapy. However other studies in the United States have shown a variation in the incidence of local and systemic reactions associated with immunotherapy but no reports of death.[4-6] A retrospective study by questionnaire for the period 1954 to 1984 by Lockey et al[7] revealed six deaths from skin testing, all had intradermal skin tests; and 24 deaths associated with allergen immunotherapy. Considering that several million people receive skin testing and immunotherapy each year, the reported incidence is very low.

The objectives of this study were to review the number and type of the local and systemic allergic reactions after skin testing and immunotherapy at the ENT Allergy Clinic, Siriraj Hospital, Bangkok, and to identify the possible factors associated with severe systemic allergic reactions after allergen immunotherapy in our practice in order to reduce their incidences in the future.

MATERIALS AND METHODS

Patients

This was a retrospective review of the medical records of adult patients who attended the ENT Allergy Clinic, Siriraj Hospital in Bangkok from January 1987 to December 1999, to identify patients who developed excessive local or systemic reactions after allergen skin tests and immunotherapy.

Skin test methods

Skin prick test was performed on the ventral surface of the forearm by placing one drop of each allergenic extract 3 cm apart, then the skin was pricked using a 26-gauge disposable needle. The intradermal skin test was performed by injecting 0.02 ml of allergen extract intracutaneously using a sterile disposable tuberculin syringe and a 26-gauge needle.

The skin test reaction was measured and recorded 15-20 minutes thereafter. The interpretation of the results of the skin prick test was based on the criteria suggested by Wormald[9] and for an intradermal skin test the criteria suggested by Vanselow[10] were used.

Allergen immunotherapy

An injection protocol starting with 0.05 ml of 10 PNU/ml of each allergen was used and this was increased gradually each week until the maximum tolerated dose was reached after which the injection interval was increased to 2, 3 and 4 weeks respectively. A maintenance dose was injected every 4-6 weeks for 3-5 years.

Allergen extracts

The aqueous extracts of common aeroallergens, e.g., house-dust mite, cockroach, grass, weed and tree pollen, molds, and cat and dog dander were used. Most of them were purchased from Greer Laboratories Inc. (Lenoir, NC) and Center Laboratories (Port Washington, NY). Some of them were prepared in-house.

For the skin prick test, the extracts contained 10,000 PNU/ml and were 50% glycerinated except for the house-dust mite extract of which the concentration used was only 5,000 PNU/ml. For the intradermal test, the concentration of the extracts was 1,000 PNU/ml and was 100 PNU/ml for the house-dust mite.

Systemic allergic reactions

Possible systemic reactions after skin testing were observed and recorded by the clinicians in the ENT Allergy Clinic. Subjective complaints including pruritus, feeling of chest tightness or dizziness, and objective findings such as urticaria or angioedema, ocular and nasal signs, cough, wheeze and/or tachycardia were recorded. Additional signs of anaphylaxis such as laryngeal edema and hypotension were also recorded. It is noteworthy that vasovagal events can occur during skin testing and should be differentiated from an allergic reaction.

For immunotherapy, adverse reactions were mainly allergic which were divided into local and systemic reactions. Local reactions were subdivided into (1) an immediate wheal and flare which developed fully within 30 minutes with a wheal diameter greater than 3 cm, and (2) a delayed subcutaneous swelling with itch at the injection site, which developed fully within 18 hours and which was greater than 5 cm. Systemic reactions from immunotherapy were classified as mild, moderate and severe "life threatening" reactions or anaphylaxis.[11,12]

A prospective study was also performed from January 2000 to December 2001, to record the incidence of systemic reactions after allergen immunotherapy and to identify possible causative factors.

RESULTS

Over a 13-year period, 5,879 adult patients were skin tested initially by the skin prick method. Intradermal testing was performed later in 5,490 patients using only the allergens which showed no reaction or an equivocal reaction during skin prick testing.

Routine skin prick testing included about 14 allergen extracts thus altogether 82,306 skin tests were performed with no systemic reactions observed. Therefore the rate of systemic reaction to skin prick testing was zero.

For intradermal testing, an average of 20 allergen extracts were tested in each patient thus 109,800 skin tests were performed. Two patients developed a mild systemic reaction which was probably related to the test. The rate of systemic reaction to intradermal skin testing was therefore 36.4 per 100,000 patients or 2.2 systemic reactions per 100,000 intradermal tests.

The overall reaction rate to allergy skin tests (prick test followed by intradermal test if skin prick test was negative or equivocal) in 11,369 patients evaluated for respiratory allergies (rhinitis and/or asthma) was 0.018% or 17.6 systemic reactions per 100,000 patients.

Concerning immunotherapy, 42,810 allergen injections were recorded. The rate of excessive local reactions was 4.83% of which 4.06% were immediate and 0.77% were delayed types. The rate of systemic allergic reactions after immunotherapy was 0.08%. None of the reactions was fatal.

During the two-year period of our prospective study, there were 4,764 allergen injections and 27 systemic reactions occurring in 23 patients (7 men and 16 women). Twenty-two events were classified as mild to moderate (0.46%) and 5 events were acute severe reactions (0.11%). No cases of hypotension or laryngeal edema were observed.

Women and men showed a roughly equal incidence of systemic reactions (0.57% and 0.56% of total female and male patients respectively). Even when only acute severe reactions were considered, these severe reactions occurred equally in men (0.08%) and in women (0.11%).

All systemic reactions responded to standard treatment, mostly with a subcutaneous injection of adrenaline, antihistamines and/or corticosteroids. None of the reactions was fatal.

Possible factors associated with systemic reactions in this group of patients were identified and divided according to the severity of the reactions and shown in Table 1.

Regarding allergens induced systemic reactions, all of the reactions were associated with pollen (91.3% grass and 60.9% weed pollen extracts). The second most common allergen was house-dust mite. This was the same for both acute severe and mild to moderate reactions.

Table 1. Possible factors associated with systemic reactions after allergen immunotherpy in ENT Allergy Clinic, Siriraj Hospital during the period 2000-2001. (4,764 injections with 27 systemic reactions occurred in 23 patients).

Possible factors	Severity of systemic reactions	
	Severe n/N (%)	Mild-moderate n/N (%)
Type of allergen in vaccines :		
Pollen	5/5 (100)	18/18 (100)
House-dust mite	3/5 (60)	14/18 (77.8)
Increased dose	4/5 (80)	5/18 (27.8)
Asthma	3/5 (60)	11/18 (61)
Prior systemic reactions	2/5 (40)	6/18 (33.3)
New vial	1/5 (20)	3/18 (16.7)

Eighty percent of the acute severe allergic reactions occurred when patients were receiving increasing doses of allergen.

Concomitant asthma was a frequent findings in both groups. Other factors such as a history of previous systemic reactions and changing to a new vial were also found.

Regarding onset of systemic allergic reactions, approximately 40% of the systemic reactions occurred within 30 minutes of the injection and another 13% developed within one hour. When only acute severe reactions were taken into consideration, 80% of them happened in the first 30 minutes.

DISCUSSION

The incidence of systemic reactions associated with allergy skin tests in our clinic was similar to the incidence reported from Pittsburgh which gave a rate of 19 systemic reactions per 100,000 patients tested.[13]

Recently a study from the Mayo Clinic, U.S.A. also showed that the systemic reaction rate for aeroallergen skin testing was 15 to 23 reactions per 100,000 skin tests or 0.015-0.02%.[14] They also found that the difference between the rates of systemic reactions to intradermal tests and to skin prick tests were not statistically significant while earlier studies[8,15] suggested that intradermal tests carried a greater risk of systemic reactions than skin prick tests.

Table 2 shows the rate of systemic reactions after allergy skin testing in various reports compared to this study.

These data have confirmed that allergy skin testing is safe especially when using the prick test method, but this is limited to aeroallergens. Skin prick tests to other allergens, such as latex and food have been reported to be associated with acute severe systemic reactions.[16,17]

Allergy skin tests are recommended universally as the most clinically applicable technique in the assessment of allergic patients.[18,19]

Concerning immunotherapy, since a high dose of allergen extract is significantly related to a greater improvement in symptoms, injection with the maximum tolerated dose is required. Therefore the chance of giving too high a dose exists and reported systemic reactions including death associated with immunotherapy are more frequent than with skin testing.

As cited before, in the questionnaire survey of Lockey et al[7] there were 24 deaths during 1959 to 1984 while there were only 6 deaths associated with intradermal skin tests in the same period. In a subsequent questionnaire survey by Reid et al[3] in the years 1985 to 1989, no fatalities were reported with skin testing while there were 17 fatalities from immunotherapy. However, when considering that an estimated 47.1 million allergen doses were given in the United States during that period, the annual

Table 2. The rates of systemic reactions to skin test reported in various journals.

Author	Year published	Systemic reactions after skin test		
		Rate	% of SPT	% of ID
Lin, et al[13]	1993	19:100,000 pts	0	0.019
Valyasevi, et al[14]	1999	15-23:100,000	0.03	0.055
Bunnag, et al	2002	17.6:100,000	0	0.036

SPT = skin prick test, ID = intradermal test, pts = patients

Table 3. The rates of systemic reactions after allergen immunotherapy reported in various journals.

Author	Year published	Systemic reactions after immunotherapy (%)
Greenberg, et al[5]	1986	7
Davis, et al[6]	1992	14.06
Lin, et al[13]	1993	2.9
Cook, et al[12]	1994	0.03
Bunnag, et al	2002	0.08

fatality rate was only one for every 2.8 million injections.

The rates of systemic reactions associated with allergen immunotherapy reported in various journals compared with this study are shown in Table 3.

Asthmatic patients are a high-risk group for developing systemic allergic reactions especially when the symptoms are uncontrolled or during an allergy season. In our study, 60% of our patients who had a systemic reaction after immunotherapy (either mild-moderate or severe) also had concomitant asthma and they were symptomatic prior to injection. Despite we do not have a definite active allergy season as in western countries, active asthmatic symptoms should be noted and the injection must be postponed.

All of our patients who underwent immunotherapy had a high degree of sensitivity as judged by the results of skin testing and 40% of patients who developed severe reactions and 27.3% of patients who had mild to moderate reactions had a history of previous systemic reactions, therefore this is a high risk factor too.

The type of allergen in the vaccine also determined the incidence of systemic reactions, e.g. pollen (grass and weed), house-dust mite. In Thailand although the common grass and weed pollen are not the same species as in the west, we also found that the vaccine which was associated with all the systemic reactions comprised grass and weed pollen, while house-dust mite was the second most common allergen.

For patients who are in the dose escalation phase, dosage errors and changing to a new vial are reported in the literature as possible risk factors for systemic reactions. In our practice, we have experienced dosage errors, either because the wrong dose was given or a wrong vial/concentration, was used. These were very rare and fortunately they did not cause any systemic reactions. But increasing doses were associated with a severe reaction in 80% of our patients who experienced a systemic reaction.

Changing to a new vial used to cause systemic reaction in few cases during the first years of our practice. After noting this we always reduce the dose when opening a new vial so the incidence of systemic reactions associated with this factor is very rare now.

Patients with cardiovascular disease and those taking beta-blocking agents are not by themselves at high risk of developing systemic reactions, but if a systemic reaction does occur it may be more severe and refractory to treatment with adrenaline, so we always ask about this factor. However, none of our patients who had systemic reaction in this report were taking beta-blockers.

The onset of systemic reactions varies in previous publications. Stewart and Lockey in 1992[20] analysed 38 reports concerning systemic reactions and noted that most of the systemic reactions started within 20 minutes of injection. Our presented data showed that 80% of the severe systemic reactions occurred within the first 30 minutes.

The Committee on Safety of Medicines in England found that the onset of a fatal systemic reaction in two of their fatalities occurred between 31 and 90 minutes after an injection of allergen extracts.[1] Therefore, they recommended that patients should be kept under medical supervision for at least two hours after an injection of allergen extract. This long waiting period is unacceptable to most patients and wide experience in the United States is not the same as the U.K. experience. Therefore in 1990, the American Academy of Allergy and Immunology recommended a 20-minute waiting period after allergen skin testing and immunotherapy.[21] Later on a 30-minute waiting period was recommended in several guidelines[22-24] and is now practised widely.

We have adopted a 30-minute waiting period for the allergy clinic in our hospital for some years and request that the patient waits for a longer period if he/she falls into a high risk category.

In a literature review of eight articles about the safety of allergen immunotherapy by Cook and Farias in 1998[25] and the current update on specific immunotherapy[26], both have concluded that allergen immunotherapy is a safe form of therapy with a very low incidence of systemic allergic reactions and fatalities. This conclusion has confirmed the recommendation for the use of allergen immunotherapy in Europe and worldwide.[23,24,27,28]

The prevalence of allergic diseases especially, allergic rhinitis and asthma is increasing constantly in all countries including Thailand.[29-31] They are now considered the most common cause of chronic illness in industrialized countries. Therefore more attention should be paid to the development and the use of specific allergen immunotherapy which is a form of disease-modifying therapy so that the allergic patients have a chance to be cured.[32]

In conclusion, we have found from our experience in this study that allergen skin testing and immunotherapy are safe procedures. A very low incidence of systemic allergic reactions is associated with intradermal testing and immunotherapy with no fatalities. The risk factors for developing a systemic reaction during immunotherapy in this study were : vaccines comprised of pollen particularly grass/ weed and house-dust mite, an increased dose, asthmatics who were symptomatic at the time of injection, prior systemic reactions, and changing to a new vial. In order to minimize the number and the severity of systemic reactions, an allergen injection should be performed by physicians or personnel who are well aware of the risks and well trained to recognize and manage systemic reactions early on. Properly administered allergen vaccines will desensitise allergic patients by modifying their immune system without the risk of severe systemic reactions.

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