

Systemic reactions to specific immunotherapy in children with respiratory allergy: a prospective study

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The aim of this multi-centre prospective study was to evaluate the prevalence of systemic reactions to specific immunotherapy in children with allergic asthma and/or rhinitis. One thousand and fifty-six children (653 boys and 403 girls), median age 8.5 years, were enrolled in this three-year prospective study. All the children were treated with injections of the following allergenic extracts: 689 of house dust mite, 291 of grass, 109 of *Parietaria*, 13 of *Alternaria*, 6 of *Artemisia* and 11 of *Olea*. Among 1056 treated children, 41 (3.7%) had systemic reactions: 40 children (3.7%) experienced mild symptoms such as asthma and/or urticaria, and only one shock (0.08%). A total of 47,247 injections were administered, and the rate of systemic reactions, according to the number of total injections was only 0.08%. According to the allergenic extract, systemic reactions occurred in 29/689 children (4.2%) treated with house dust mites extract (0.09% of the injections), in 9/291 children (3.1%) treated with grass extract (0.07% of the injections) and in 3/109 children (2.8%) treated with *Parietaria* extract (0.06% of the injections). The prevalence of systemic reactions was significantly higher ($p < 0.0001$) in the children treated with house dust mite extract in comparison with those treated with pollen extracts. All the systemic reactions appeared within 30 minutes following the administration of the extract and occurred in 37/41 cases (90.2%) with the same dose, previously tolerated. Most reactions were mild, and were readily controlled by immediate emergency treatment. There was no need for hospitalization. The low prevalence of systemic reactions (0.08% of the total injections and 3.7% of the total treated, indicates that specific immunotherapy with inhalant allergens is safe in children with respiratory allergic diseases.

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Systemic reactions to specific immunotherapy (SIT) have been reported since 1911, when this therapy was introduced into clinical practice (1), and subsequently many other reports have discussed the occurrence of such reactions (2–8). A number of fatalities after SIT have been also rarely reported, since Lamson in 1929 first described a death from anaphylaxis after SIT (9–11). The prevalence of systemic reactions in adults has been estimated between 5% and 44% for grass SIT (12–14), and between 7 and 50% for mite SIT (4, 8, 15), whereas at present there are a few data in children (16, 17). According to these studies performed on a small number of children with asthma, systemic reaction rate was actually zero using a mite extract (16), and

between 80 and 100% using a highly purified and standardized mold extract (17).

The aim of this study was to evaluate the prevalence of systemic reactions to SIT in a large number of children with asthma and/or rhinitis.

Material and methods

We have enrolled in this prospective study 1,056 children who consecutively underwent SIT between 1st January 1987 and 31st December 1989, 653 boys (62%) and 403 girls (38%), median age 8.5 years (range 4–16.5 years). The clinical characteristics of the children are as follows: 516 children suffered from asthma (50%), 37 from perennial rhinitis (3%)

Table 1. Characteristics of the 1056 children enrolled in the study

Sex	Male:	653
	Female:	403
	Median age 8.5 years (range 4–16.5 years)	
Clinical aspects	Asthma:	No 516
	Rhinitis:	No 37
	Hay fever:	No 125
	Asthma and rhinitis:	No 378

125 from hay fever (12%) and 378 from asthma and rhinitis (35%) (Table 1). Specific Immunotherapy was prescribed by the authors of the present study in the Allergic Clinics of the Departments of Pediatrics of the following Universities: "La Sapienza" of Rome, University of Cagliari, University of Catania, University of Milano, and of the Hospital S. Spirito of Bra. Specific Immunotherapy was prescribed and administered according to the guidelines of the Allergy and Clinical Immunology Committee of the Italian Society of Paediatrics (7) which is similar to that of EAACI (18). The allergenic extract for SIT contained a single allergen: grass, or parietaria, or artemisia or dermatophagoides pteronyssinus (Dpt) and/or farinae. Patients with clinical sensitization to two different allergens (63 cases) received 2 extracts, each prepared with one allergen. The allergenic extracts were provided by the following Laboratories: Anallergo (Florence); Bracco-Linea Allergopharma (Milan); Bayropharm Italiana, Allergen Division (Milan); Istituto Sieroterapico Milanese (Milan); Kallergen (Settimo Milanese); Laboratorio Farmaceutico Lofarma (Milan); Neo-Abello (Milan); Pharmacia (Cologno Monzese); SARM Allergeni (Guidonia). Most allergenic extracts were standardized in BU or SQ (19) Specific immunotherapy was prescribed and administered by the authors of this study, or occasionally by other physicians, supervised by the same investigators. The top dose was gradually reached and varied according to the patient's clinical status and sensitivity. As a mean, it was 500 BU/month. Exclusion criteria for the injections were: recent respiratory infection, current asthma, and every acute condition, i.e. fever, vomiting, diarrhea, etc. Detailed precautions were given to all participating doctors in order to minimize the risk of errors in the administration of SIT. The children were observed for 30 minutes following the treatment according to recent guidelines (18, 20–22). Facilities for emergency treatment were at immediate disposal. The doctor has to record on a special chart the date, the administered dose the type of systemic reaction, the time of onset of symptoms, the severity of the systemic reaction (score 1–3), its duration and the type of emergency treatment and the outcome.

Table 2. Type of allergenic extract administered

Allergenic extract	No. cases
Dermatophagoides pt. and/farinae	689
Grass	291
Parietaria officinalis	109
Alternaria	13
Artemisia	6
Olea	11

Statistical analysis

The X2 and the expected frequencies tests were employed.

Results

There was a total of 1,119 treatments with the following allergenic extracts: 689 for mite, 291 for grass, 109 for parietaria, 13 for alternaria alternata, 6 for artemisia and 11 for olea (Table 2). A total of 47,247 injections were performed. Of the 1,056 treated children, 41 had systemic reaction (3.7%) in particular asthma and/or urticaria in 40 cases (3.6%) and 1 case of systemic anaphylaxis (0.08%). The prevalence of systemic reactions, according to the allergenic extract, are reported in Table 3. It is evident from the Table that mite extracts triggered a significant higher number of systemic reactions than that of pollen extracts ($p=0.000$, observed vs. expected frequencies $p=0.000$). The systemic reactions occurred within 20 min or less in all children. In 37/41 children (90.2%) the reactions occurred with the maintenance dose, previously well tolerated, and only in 4/41 cases (9.8%) the reaction occurred during dose build-up. The only case of anaphylactic shock occurred within a few seconds of the injection of the maintenance dose of the mite extract (400 BU) administered by one of us (LB), in an 8-year-old boy suffering from asthma. The same dose was previously injected 4 times, without reaction. The anaphylactic shock was successfully treated with prompt use of epinephrine and hydrocortisone. The children remained under medical supervision in the Clinic for 12 h. There was no need for hospitalization. Systemic reactions were success-

Table 3. Prevalence of systemic reaction according to the type of allergenic extract

Extract	Systemic reactions			
	No. cases	(%)	No. injections	(%)
Mite	29/689	(4.2)	29/29,091	(0.09)
Grass	9/291	(3.1)	9/12,286	(0.07)
Parietaria	3/109	(2.8)	3/ 4,602	(0.06)

$p=0.0000$ mite vs pollens (grass and parietaria).

fully treated in all patients with prompt use of epinephrine, cortisone and/or β -2-agonists, or antihistamines, according to clinical presentation. However, most reactions were controlled only by oral antihistamines, and there was no need for hospitalization.

Discussion

This study, performed on a large population of children 85% with allergic asthma and 15% with hay fever or perennial rhinitis, shows a low prevalence of systemic reactions to SIT. Forty one of 1,056 children (3.7%) (41/47,247 injections = 0.08%) experienced systemic reactions; 40/41 children experienced asthma and/or urticaria, whereas only 1 child had anaphylactic shock. However, we point out that in this study SIT was administered by the prescribing pediatric allergist, and only to some patients by a non-allergist primary practitioner, always supervised by the prescribing pediatric allergists, and instructions covering detailed precautions were given. This may have minimized the risk of systemic reactions. The pretty good outcome of the systemic reactions due to prompt, appropriate treatment strongly indicates that SIT is safe when administered by a well trained physician. Specialists in allergy are trained to modulate the dose of the allergenic extract according to different situations, such as patient sensitivity, bronchial hyperreactivity, current asthma, severity of symptoms and allergen exposure, thus remarkably reducing the risk of systemic reactions. In addition, they are both trained to recognize the premonitory symptoms of anaphylaxis and to promptly handle anaphylaxis if it occurs.

Several risk factors for systemic reactions have been recently identified: some are related to the patient (symptomatic asthma, recent respiratory infection, bronchial hyperreactivity), whereas others are related to the environment (allergen exposure, such as during the pollen season) or to errors in the administration of SIT: inadvertent errors in dosage, inadvertent intravenous administration, inappropriate dose increase despite recent symptoms or prior systemic reaction, switch to a new vial extract, dosing during the allergen season (7, 10, 11, 23). Although the enrolled children received SIT even during the pollen season when the allergen exposure was maximum, no systemic reactions occurred. In addition, no systemic reaction could be associated with allergen exposure in all cases who experienced systemic reactions. Recent respiratory infections and current asthma were exclusive criteria from infection as well as acute affection. Therefore, the careful examination of the children each time before injection played a significant role in minimizing the systemic reaction prevalence.

Nevertheless, despite all precautions, systemic reactions may occur at any time in the course of SIT, even when the patient has been receiving the same maintenance dose of extract for years, and even when SIT is appropriately administered (7, 10, 11, 23). In the present study, systemic reactions occurred in 37/41 patients (90.2%) with the maintenance dose, previously tolerated, and only in 4/41 patients (9.8%) during dose buildup. Again, the only case of shock occurred in a child who received the same dose, previously tolerated for several months. In other studies in adults, most systemic reactions occurred during dose build-up (4, 8). According to previous surveys (4, 11, 23), this study shows that mite extract triggered a significant higher number of systemic reactions ($p=0.0000$) in comparison with pollens extract. Although several studies have demonstrated the relative safety of SIT (18), it is imperative that the occurrence of severe reactions are reduced to a minimum. A retrospective study performed by Lockey et al. (10) in the USA showed that over the period 1945–1985 46 deaths to SIT or intradermal skin tests occurred. More recently, 17 fatalities associated with SIT for the years 1985–1989 were reported from members of the American Academy of Allergy and Immunology (23). Three of the 17 patients who died were children (23). Onset of anaphylaxis occurred within 30 min in all the patients but one (23). Also in this survey the risk of fatal reactions appears to be increased in patients with asthma and the risk is further increased when the patient with asthma is steroid-dependent; has required hospital or emergency room visits for treatment; is experiencing increased bronchospasm; or has compromise of another vital system (e.g. cardiovascular) (23). It has been shown by the Committee on Safety of Medicines that 26 deaths due to SIT occurred between 1957 and 1986 in England (11).

These surveys have confirmed the risk factors for systemic reaction, previously mentioned. The time of onset of systemic reactions is a matter of great importance, because it defines the appropriate waiting period in the office following the injection (19, 23). In our study, all the systemic reactions occurred within a few minutes after the administration of SIT. Levine (3) reported that 50% of systemic reactions occurred within 30 minutes following the administration of the extract. In the 63 deaths reported in the USA over 29 years, shock occurred within 20 min in 27 cases, between 20 and 30 min in 2 cases and after 30 min in 4 cases, whereas there was no information available for the other cases (10, 23). The UK Committee on Safety in Medicines recommends that patients remain under medical observation for 2 h after the administration of SIT (11) because among the 26 reported deaths: 76% occurred within 20 minutes; 15% between 20 and 120 min; 4% between 2 and 4

h; and 4% between 6 and 36 h (11). The causal relationship between SIT and fatalities becomes less convincing when the onset of symptoms occurs several hours following the injection. The administration of SIT, according to this recommendation, is extremely difficult or even impossible. However, the Executive Committee of the American Academy of Allergy and Clinical Immunology recommends an observation period of 20 min (20). This period may be increased for high-risk patients. Recently, the Working Group of the International Union of Immunological Societies and the WHO recommended keeping patients under medical observation for 30 min (21). Most of the deaths from anaphylactic shock can be avoided if SIT is administered, or carefully supervised, by a well-trained allergist (7, 24). The prompt availability of equipment and medicine for emergency treatment and physicians drilled in the treatment of anaphylaxis are mandatory for the correct management of systemic reactions (24). The equipment must be listed and checked every week and the expiry date of the medicines should be noted in order to provide for their substitution. The prompt recognition of systemic reactions and the immediate use of epinephrine are the mainstay of management of systemic allergic reactions.

In conclusion, our study indicates that SIT triggers in children a low prevalence of systemic reactions. However, in order to minimize risk of serious reactions and to handle anaphylaxis, should it occur, SIT should be prescribed, and supervised by allergists, and administered only by physicians skilled in the management of anaphylaxis.

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