A Prospective Study of Asthma Desensitization in 1,182 Children 592 Asthmatic Children and 590 Nonatopic Controls

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Introduction
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 to 100% using a highly purified and standardized mold extract [17].

Exposure to high levels of allergen during early life might contribute to the rising prevalence of pediatric asthma. Dramatic worldwide variations in asthma prevalence have been found especially of severe forms of asthma, whose frequency is unknown. The aim of this study was to evaluate the results of the desensitization to respiratory allergens in a large number of children with asthma and/or rhinitis. We also discuss the issue of possible systemic reaction during SIT administration.

Materials and Methods
During 2003, we have consecutively enrolled all children ranging in age from 3 to 11 years attending our Division because affected with severe asthma. Inclusion criteria were as follows physical examination, positive skin-prick test (SPTs), specific IgE (sIgE) to inhalant allergens, and spirometry. Controls were 590 non atopic children matched for age and sex recruited from our outpatient clinic. The study children were treated with personalized asthma desensitization; the controls were treated with usual medications. The parents of all children gave their informed consent. Data were analyzed using the X2 method. Children were observed for 30 minutes following the treatment. Facilities for emergency treatment were at immediate disposal. The doctor had 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. Kendall’s method was used for the statistical analysis.

Results
The study included 1,182 children, The 592 atopic children with severe asthma, 370 males and 222 females, aged 2.5 to 7.5 years, (mean 3.9 years) tested positive for Der p and Der f (47.1%) or for pollen allergens (52.9%). During 2001 there were 135 such children and 215 during 2002, with a 62.5% increase. During 2003 there were 242 children, with a 88.8% increase compared to 2002. All of these children were subjected to asthma desensitization, previously specific immunotherapy (SARM, Roma). At the second yearly control, the study children had a significantly greater reduction as regards days (p = 0.0001) and nights (p = 0.0005) without asthma and drug usage (p = 0.0003) compared with drug-treated children. The number of SPTs and/or sIgE to inhalants also decreased, spirometry data were also notably improved. We have recorded no severe systemic reactions; The clinically adverse events only were mild or transient.

Discussion
This study, performed on a large population of children, 85% with allergic asthma and 15% with hay fever or perennial rhinitis, shows a zero prevalence of systemic reactions to SIT. 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 hyper reactivity, 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 hyper reactivity), 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 al·lergen season [7,10,11,18]. 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 exclusion criteria from injections, as well as any other 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 [7,10,11,18]. 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 build-up. 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 [4,11,18], this study shows that mite extract triggered a significant higher number of systemic reactions (p < 0.0001) in comparison with pollens extract. Although several studies have demonstrated the relative safety of SIT [19], it is imperative that the occurrences of severe reactions are reduced to a mini-mum. A retrospective study performed by Lockey et al. [10] in the U.S.A. showed that over the period 1945-1985 46 deaths to SIT or intra dermal 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 [18]. Three of the 17 patients who died were children [18]. Onset of anaphylaxis occurred within 30 minutes in all the patients but one [18]. 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 broncho spasm or has compromise of another vital system (e.g. cardiovascular) [18]. 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 [20,21].

Asthma de·sensiti·za­tion is the only one that may modify the natural course of allergic asthma, since it interferes with the underlying immunological mechanism. Such intervention in early life may modi-fy the de·ve·lopment of the immune response to allergens. The positive re­sults obtained in this large study add to its safety in our opinion because the children were followed by their doctors also on the basis of “as frequently as needed”. Accordingly, the early onset of childhood asthma emphasizes that an early treatment is the only means to significantly abate the march of atopic asthma. The causes of this dramatic increment (10.4%/month in the last six months) may be iden-tified chiefly in the world-wide increase in air pollution and secondhand tobacco smoke.. Levine (2) reported that 50% of systemic reactions occurred within 30 minutes following the administration of the extract. In the 63 deaths reported in the U.S.A. over 29 years, shock occurred within 20 minutes in 27 cases, between 20 and 30 minutes in 2 cases and after 30 minutes in 4 cases, whereas, there was no information available for the other cases [10,18].

The UK Committee on Safety in Medicines recommends that patients remain under medical observation for 2 hours after the administration of SIT [11] because among the 26 reported deaths: 76% occurred within 20 minutes; 15% between 20 and 120 minutes; 4% between 2 and 4 hours; and 4% between 6 and 36 hours [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, accord-ing 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 minutes [19,21]. This period may be increased for high-risk patients. Recently, the Working Group of the International Union of Immunological Societies and the W.H.O. recommended keeping patients under medical observation for 30 minutes [22]. Most of the deaths from anaphylactic shock can be avoided if SIT is administered, or carefully supervised, by a well-trained allergist [7,23].

The prompt availability of equipment and medicine for emergency treatment and physicians skilled in the treatment of anaphylaxis are mandatory for the correct management.
of systemic reactions [23]. 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.

Conclusion

In conclusion, our study indicates that SIT has desensitized a great number of asthmatic children. Several studies by ours demonstrate that no immediate reaction occur when SIT is prescribed, and supervised by allergists, and administered only by physicians skilled in the management of anaphylaxis [24-30].

References