

Frequency and intensity of late asthmatic reactions after bronchial allergen challenge in asthma and rhinitis

W. J. STEVENS & H. P. VAN BEVER

Immunology and Pediatrics, University of Antwerp, Belgium

The occurrence of late asthmatic reactions after bronchial allergen challenge was studied in 50 house dust mite allergic patients subdivided in three groups: one group had asthma without nasal symptoms, another group had rhinitis without pulmonary symptoms and a third group had a combination of both asthma and rhinitis. Late asthmatic reactions were present in 80% of asthmatic patients and in 18.7% of rhinitis patients. The degree of non-specific bronchial reactivity to histamine (provocative dose 15 or PD15 histamine) and the degree of immediate reactivity to allergen (PD15 house dust mite) did not differ significantly between patients with and without late asthmatic reactions. These findings suggest that an important difference between asthma and rhinitis is the lack of late asthmatic reactions in rhinitis patients, whereas the degree of immediate bronchial reactivity to the allergen is similar in asthma and rhinitis.

Key words: allergen; asthma; challenge; house dust mite; immediate asthmatic reaction; late asthmatic reaction; late phase reaction; rhinitis.

Accepted for publication 28 April 1989

CLINICAL ASPECTS

Clinicians often wonder why in patients with the same type of respiratory allergy, some develop asthma and some develop rhinitis. Non-specific hyperreactivity of the bronchi is present in both asthma and rhinitis but is more severe in asthma than in rhinitis. Nevertheless, for the individual patients overlap exists in the degrees of non-specific hyperreactivity between asthma and rhinitis. We have studied late asthmatic reactions (LAR) after bronchial allergen (house dust mite) challenge in patients with allergic asthma or rhinitis. Asthma is associated with LAR in 80% of the challenges whereas rhinitis in only 19%. The ability to develop LAR might be an important hallmark of asthma.

The occurrence of late asthmatic reactions (LAR) after bronchial allergen challenge better reflects the clinical signs and symptoms of asthma than immediate asthmatic reactions (IAR) (3). In an earlier study we reported our findings on the degree of non-specific and specific bronchial reactivity after histamine and allergen challenge in patients with asthma and rhinitis (8). In that study, it was found that, although the degree of non-specific bronchial reactivity to

histamine differed significantly between asthmatic and rhinitis patients, there was no difference in the degree of specific reactivity to grass pollen or house dust mite between asthmatic and rhinitis patients. It was concluded that the IAR to allergen in asthma and rhinitis reflected only the sensitization of the bronchial tree to the allergen, but that it was probably the degree of non-specific hyperreactivity which determined a patient being an asthmatic or rhinitis

Table 1
Descriptive data of patient groups

Patient group	Age (years)	Initial FEV ₁ % of predicted	Serum IgE kU/l	Eosinophils per μ l
Asthma	22.3 $\pm$ 11.4	86.4 $\pm$ 11.4	380 5.94 $\pm$ 0.65	242 5.49 $\pm$ 1.03
Asthma and rhinitis	17.3 $\pm$ 8.1	89.7 $\pm$ 11.2	228 5.43 $\pm$ 0.93	337 5.82 $\pm$ 0.71
Rhinitis	21.8 $\pm$ 12.4	100.2 $\pm$ 14.7	279 5.63 $\pm$ 1.12	270 5.60 $\pm$ 0.90

Serum IgE and eosinophils are presented as the geometric mean and the mean $\pm$ SD of the logarithmic values (natural logarithm)

patient. Although known for several years (5), the importance of LAR in asthmatics has been reemphasized recently. Some authors reported that LAR corresponded better with the severity of asthma (6, 10), while others could not confirm this relationship (1). It has also been demonstrated that the LAR is associated with increased non-specific bronchial hyperreactivity (2, 4). Further, LAR tended to disappear during allergen hyposensitization (7, 9, 11). In this study we evaluated LAR in patients with asthma and/or rhinitis after bronchial allergen challenge in order to compare the frequency and magnitude of these LAR between asthmatic and rhinitis patients.

MATERIAL AND METHODS

Patients

Fifty patients (mean age 19.7 years, range 8–42) were studied. According to the presenting signs and symptoms, which were evaluated by meticulous history taking and clinical examination, the patients were subdivided into those with asthma ($n = 10$), when only pulmonary symptoms of recurrent wheezing and cough were present. A spirometrically demonstrable decrease of FEV₁ of 20% of the theoretical values had to be reversible by inhalation of beta₂-sympathomimetics. Rhinitis ($n = 16$) was diagnosed when recurrent nasal symptoms of sneezing, itching, runny nose and nasal blockade occurred alone or in association, and

when no pulmonary symptoms of wheezing or cough were present. Asthma and rhinitis ($n = 24$) were diagnosed when patients had both pulmonary and nasal symptoms. To compare bronchial challenge results between groups, only those with mild asthma were studied during a relatively asymptomatic period, when they could stop antiasthmatic drugs prior to challenges. This is why the initial FEV₁ before antigen challenge did not differ significantly between the three groups (asthma: 86.4 $\pm$ 11.4% of predicted, asthma and rhinitis 89.7 $\pm$ 11.2, and rhinitis 100.2 $\pm$ 14.7%).

All patients had a history suggesting positivity to house dust mite (*Dermatophagoides pteronyssinus*). Skin testing and specific IgE determination via RAST (Pharmacia, Brussels, Belgium) confirmed positivity in 48/50 patients. One asthmatic and one patient with both asthma and rhinitis had negative skin tests and RAST for house dust mite. Neither patient had an immediate reaction to allergen challenge but only a late reaction. Total blood eosinophils and total serum IgE (PRIST, Pharmacia, Brussels, Belgium) were also measured.

Methods

Bronchial allergen and histamine challenges were performed as described earlier (8). Briefly, patients had stopped antihistamines at least 3 days prior to bronchial challenge (no patients were using the long-acting antihistamine, astemizole), beta₂-sympathomimetics and cromol-

glycate at least 12 h, and long-acting theophylline at least 24 h before testing. No patients were using corticosteroids either orally, parenterally or inhaled. A standardized procedure was used for the challenge tests. After establishing baseline values for peak expiratory flow (PEF) (mini peak flow meter, Wright, UK) VC and FEV₁ (OHIO dry spirometer), the subjects inhaled through a mouthpiece and with the nose clipped, solutions delivered by a Bird Mark 7 respirator with nebulizer (particle size 0.5-5 µm according to the manufacturer) at an approximate mean flow of 0.9 l/s. Each patient inhaled first saline for 1 min and FEV₁ was recorded before and after inhalation to rule out irritant and non-specific responses. To evaluate non-specific bronchial hyperresponsiveness, progressively increasing two-fold dilutions of histamine hydrochloride in saline without buffer solution were inhaled for 1 min through the mouthpiece of the Bird ventilator and with the nose occluded, starting at a dilution of 0.125 mg/ml reaching a maximum of 32 mg/ml. VC and FEV₁ were measured immediately and 10 min after inhalation. Provocation was stopped when FEV₁ decreased to at least 20% from the initial value or from the best value recorded during the challenge procedure. To compare the degree of hyperreactivity between individuals, provocative dose 15 (PD15) was calculated. In a previous study (8), the lower limit of the PD15 for histamine challenge in control individuals (geometric mean minus 2 SD) was determined (5.66 mg histamine/ml). Based on this cut off level, all asthmatics and all patients with both asthma and rhinitis were hyperreactive, whereas 12/16 of the rhinitis patients showed hyperreactivity. Bronchial histamine challenge was always performed before allergen challenge.

For allergen challenge, progressively increased concentrations (10, 100, 500, 1000 BU/ml) of the same commercial allergen extract of house dust mite (*D. pteronyssinus*, Haarlem Allergen Laboratories, HAL, Haarlem, The Netherlands) that was used for skin testing, was inhaled via the same procedure for 1 min. If the decrease in FEV₁ was less than 15% after inhalation of 1,000 BU/ml, the provocation was considered negative. All individuals or their parents gave informed consent to the challenge procedure. After finishing the procedure for measuring the IAR, peak flow measurements were recorded hourly for at least 8 h, and then 24 h after the beginning of the challenge procedure or more frequently when symptoms occurred. A LAR was defined as a decrease in PEF of at least 20% in the observation period starting from 4 to 8 h after the beginning of the challenge.

Statistical analysis

The natural logarithms of PD15 and serum IgE were used as these values gave a closer approximation to normal distribution than the untransformed data. Differences between groups were studied by one-way analysis of variance or by Student t test (unpaired data) where appropriate. Differences between frequencies were evaluated by chi-square analysis and the relationship between variables was assessed by the linear regression analysis and calculation of correlation coefficient after logarithmic transformation of the data where appropriate. Differences were considered significant at the 0.05 level.

RESULTS

Table 1 presents the values of initial FEV₁, total serum IgE, and total number of blood

Table 2
Occurrence of IAR and LAR in patient groups

	IAR	IAR + LAR	LAR	A LAR (%)
Asthma (n = 10)	2	4	4	8 (80)
Asthma and rhinitis (n = 24)	12	11	1	12 (50)
Rhinitis (n = 16)	13	2	1	3 (19)

A LAR: patients with isolated LAR or LAR in combination with IAR. Chi-square 7.08 $P = 0.29$ (all), 5.66 $P = 0.017$ (AR)

Table 3

Comparison of PD15 HDM between patients with both asthma and rhinitis with isolated IAR and combined IAR and LAR

	Geometric mean (BU/ml)	Mean ln PD 15 HDM	SD
Isolated IAR (<i>n</i> = 12)	111	4.71	1.81
Combined IAR and LAR (<i>n</i> = 11)	92	4.52	2.11

eosinophils in the different groups. The groups are comparable for age, total serum IgE, and eosinophils. Initial FEV₁ is slightly higher in rhinitis patients. The occurrence of IAR and LAR is presented in Table 2.

The differences between these frequencies are highly significant (chi-square 7.08, *P* = 0.029) and remain significant when only the groups of isolated asthma and rhinitis are compared (chi-square 5.66, *P* = 0.017). From this analysis it can easily be calculated that 80 % of asthmatics have LAR (isolated LAR or LAR in combination with IAR), whereas only 19 % of rhinitis patients have LAR. The group with both asthma and rhinitis lies between (50 %).

Table 3 presents the geometric means of PD15 house dust mite (HDM) for patients with both asthma and rhinitis, subdivided according to the presence of isolated IAR or simultaneously occurring IAR and LAR. There are no significant differences in PD15 HDM between patients with IAR and IAR and LAR. Statistical analysis was only made in the group with both asthma and rhinitis since the numbers of patients in the other groups were too small for comparison.

Table 4 gives the mean values for the maximal decrease of PEF during the late reaction. The mean decrease is significantly less in pa-

tients with rhinitis compared with the asthmatic groups. This means that the late asthmatic reaction is less severe in rhinitis patients than in asthmatics.

There is no correlation between the level of total serum IgE or house dust mite-specific IgE and the decrease in PEF. Further, the mean levels of total serum IgE and house dust mite-specific IgE were not statistically significantly different between patients with and without LAR. Nevertheless, the great variability of the degree of non-specific hyperreactivity and the relatively small number of patients studied do not allow us to draw definite conclusions about this item.

There is a slight difference in the mean levels (geometric means) of PD15 HIS, measured before allergen challenge, between asthmatics (1.07 mg/ml), patients with both asthma and rhinitis (1.24 mg/ml) and rhinitis patients (1.53 mg/ml) but this difference is not statistically significant.

In Table 5 the mean levels of PD15 HIS are compared between patients with and without late asthmatic reactions.

The difference between the means is not statistically significant either. This means that patients with LAR do not have a higher degree of non-specific bronchial responsiveness than patients without LAR. Since the frequency and intensity of the LAR differs between patients

Table 4

Decrease in peak flow rates % during late asthmatic reactions in the different patient groups

	Mean	SD
Asthma	43.0	12.9
Asthma and rhinitis	35.4	10.6
Rhinitis	22.7	2.1

Table 5

Geometric means of PD HIS (mg/ml) between patients with and without LAR to HDM challenge

	Log. mean	SD	Geom. mean
Only IAR	-0.90	1.45	0.40
Any LAR	-0.65	1.34	0.52

suffering from isolated asthma and asthma associated with rhinitis, the PD15 HIS was compared between these groups (geometric means 0.32 and 0.41 mg histamine/ml respectively). The differences are not statistically significant.

DISCUSSION

In this study LAR after bronchial allergen challenge with house dust mite was observed in 80% of patients with asthma, in 19% of patients with rhinitis and in 50% of patients with both asthma and rhinitis.

The difference between these frequencies is highly significant, which means that patients with rhinitis (with or without asthma) less frequently develop a LAR than patients with isolated asthma. It was surprising that patients with both asthma and rhinitis had LAR less frequently than patients with asthma alone. It would appear that the co-existence of rhinitis prevents an asthmatic from developing a LAR. Although there is no explanation for this phenomenon, it is probably not due to the degree of specific or non-specific bronchial reactivity since there were no differences in PD15 HDM and PD15 HIS between patients who develop a LAR and patients who do not. Further, PD15 HIS did not differ between patients with isolated asthma and patients with both asthma and rhinitis. In an earlier study (8) it was stated that the degree of non-specific airway hyperreactivity determines whether an allergic individual becomes an asthma or a rhinitis patient. In this study it was shown that the LAR in the rhinitis group was less frequent and less severe than in the asthmatic groups; LAR in rhinitis patients was mild with a decrease in peak flow rate of approximately 20% ($22.7\% \pm 2.1\%$). In contrast, in asthmatics the peak flow rate decreased $43\% \pm 12.9\%$. From this study it would appear that the main difference between asthma and rhinitis lies in the ability to develop a LAR. At present there is no explanation why 19% of rhinitis patients show a LAR, but this could be due to the presence of latent cryptogenic asthma.

It has been shown that non-specific bronchial hyperreactivity can increase for some time after a LAR (2, 4). In this study, probably due to the

smaller number of patients, the difference in the degree of non-specific hyperreactivity between asthma and rhinitis, although present, did not differ significantly between groups. In contrast the frequency and severity of LAR differed very significantly. The difference in the degree of non-specific bronchial hyperreactivity between asthma and rhinitis is probably, at least in part, caused by the existence of LAR in asthma. This is in accordance with the findings of Cartier et al. (2), who reported increased histamine sensitivity of the airway after allergen challenge, strongly correlated with the magnitude of the fall in FEV_1 of the late asthmatic reaction. Nevertheless, the correlation-coefficient between the PC_{20} histamine before challenge and the fall in FEV_1 of the late asthmatic reaction calculated from their data is not significant, which is in accordance with our data.

REFERENCES

1. Booij-Noord, H., de Vries, K., Sluiter, H. J. & Orie, N. G. M.: Late bronchial obstructive reaction to experimental inhalation of house dust extract. *Clin. Allergy* 2, 43-61, 1972.
2. Cartier, A., Thomson, N. C., Frith, P. A., Roberts, R., Tech, M. & Hargreave, F. E.: Allergen-induced increase in bronchial responsiveness to histamine: relationship to the late asthmatic response and change in airway caliber. *J. Allergy Clin. Immunol.* 70, 170-177, 1982.
3. Cockcroft, D. W.: Mechanism of perennial allergic asthma. *Lancet* 2, 253-256, 1983.
4. Cockcroft, D. W., Ruffin, R. E., Dolovich, J. & Hargreave, F. E.: Allergen induced increase in nonallergic bronchial reactivity. *Clin. Allergy* 7, 503-513, 1977.
5. Herxheimer, H.: The late bronchial reaction in induced asthma. *Int. Arch. Allergy Appl. Immunol.* 3, 323-328, 1952.
6. MacIntyre, D. & Boyd, G.: Factors influencing the occurrence of a late reaction to allergy challenge in atopic asthmatics. *Clin. Allergy* 14, 311-317, 1984.
7. Metzger, W. J., Donnelly, A. & Richerson, H. B.: Modification of late asthmatic responses (LAR) during immunotherapy for Alternaria-induced asthma. *J. Allergy Clin. Immunol.* 71, Suppl. 119, 1983 (abstract).
8. Stevens, W. J. & Vermeire, P. A.: Bronchial responsiveness to histamine and allergen in patients suffering from asthma, rhinitis, cough. *Eur. J. Respir. Dis.* 67, 203-212, 1980.
9. Van Bever, H. P., Bosmans, J. & Stevens, W. J.: Occurrence of late asthmatic reaction (LAR) in children receiving immunotherapy. *J. Allergy Clin. Immunol.* 79 Suppl. 243, 1987 (abstract).

10. Warner, J. O.: Significance of late reactions after bronchial challenge with house dust mite. *Arch. Dis. Child.* 51, 905-911, 1976.
11. Warner, J. O., Soothill, J. F., Price, J. F. & Hey, E. N.: Controlled trial of hyposensitisation to *Dermatophagoides pteronyssinus* in children with asthma. *Lancet* 2, 912-915, 1978.

Address:

W. J. Stevens, M.D.
Immunology UIA
Universiteitsplein 1
B 2610 Antwerp
Belgium