

The effect of inhaled fenoterol, administered during the late asthmatic reaction to house dust mite (*Dermatophagoides pteronyssinus*)

Hugo P. Van Bever, MD,^{***} Kristine N. Desager, MD,^{***} and Wim J. Stevens, MD, PhD^{**} Antwerp, Belgium

A double-blind, placebo-controlled crossover study was set up to investigate the effect of fenoterol (400 µg) during the late asthmatic reaction (LAR). Twenty young subjects with asthma (mean age, 11.8 years; range, 8.3 to 20.6 years) were selected on the basis that they developed an LAR after bronchial challenge with Dermatophagoides pteronyssinus. After the LAR occurred, a placebo and fenoterol were administered blindly by a metered-dose inhaler, with an interval of 15 minutes and in alternating, random sequence. At the start of the study, that is, a documented LAR, the two groups of subjects had the same severity of LAR, as expressed by the fall of the FEV₁ (mean, -34.5% versus -33.5%). The mean FEV₁ of the 10 patients who received placebo first changed only -1.1% (±5.0), whereas after fenoterol, the FEV₁ increased by 20.7% (±10.8). In the 10 patients receiving fenoterol first, the mean FEV₁ rose by 18.8% (±8.0), whereas the placebo inhalation resulted in a supplementary increase of 3.1% (±7.0). The paired Student's t test between these differences (placebo versus fenoterol) was highly significant (p < 0.001). Although it was demonstrated in some studies that β-agonists did not prevent the LAR, the present study demonstrates that the administration of fenoterol can reverse the FEV₁ significantly, although it was not reversed completely, during an allergen-induced LAR. (J ALLERGY CLIN IMMUNOL 1990;85:700-3.)

It has been demonstrated that β-agonists, administered before an allergen challenge, can inhibit the IAR but have no inhibitory effect on the LAR.^{1, 2} However, in other studies, a protective effect of β-agonists on the LAR was documented.^{3, 4} In most studies β-agonists were administered before starting the allergen challenge, and since most LARs occur more than 6 hours after the allergen has been inhaled, this lack of protective effect could be due to the disappearance of the medication from the airways. Data on pharmacokinetics of β-agonists have demonstrated that after inhalation, the maximal bronchodilating effect occurs after 15 minutes, that the half-life of different β-agonists varied from 3 to 6 hours, and that the bronchodilatation persists for 4 to 6 hours.^{5, 6} To the best of our knowledge, no data are available on

Abbreviations used

IAR: Immediate asthmatic reaction
LAR: Late asthmatic reaction
Dpt: *Dermatophagoides pteronyssinus*
BU: Biological unit

the effect of β-agonists administered immediately before the LAR occurs. In a preliminary study, it was suggested that β-agonists reverse the LAR, but this was not a double-blind study and no placebo was included.⁷ In another open study, the administration of β-agonists during an LAR normalized the airway resistance in 87% of the cases,⁸ and in a study by Pepys and Hutchcroft,⁹ individual data were provided, demonstrating temporary reversibility of the LAR by β-agonists. In the state-of-the art article by O'Byrne et al.¹⁰ on the LAR, it was mentioned that β-agonists can partially reverse the LAR, but no exact data were listed on that subject.

In this study, the effect of inhaled fenoterol administered during an allergen-induced LAR was compared to the effect of placebo in a double-blind design.

From the *Departments of Paediatrics and **Immunology, University of Antwerp, Antwerp, Belgium.

Received for publication Dec. 30, 1988.

Revised June 8, 1989.

Accepted for publication June 14, 1989.

Reprint requests: W. J. Stevens, MD, Immunology U.I.A., Universiteitsplein 1, B 2610 Antwerp, Belgium.

1/1/17802

TABLE I. Individual data (FEV₁ expressed in liters and percent of predicted value for height)

Group 1 (placebo—10 min—fenoterol)				
Patient	Basal FEV ₁ (%)	LAR	After placebo	After fenoterol
D. M.	1.90 (85)	1.35	1.33	1.74
P. J.	2.00 (84)	1.18	1.06	1.47
D. S. T.	3.56 (96)	2.42	2.68	3.23
P. M.	1.92 (96)	1.07	1.10	2.00
B. K.	1.57 (93)	0.90	0.89	1.20
D. B. T.	2.17 (98)	1.38	1.34	1.66
W. B.	2.76 (98)	1.70	1.46	2.34
P. G.	1.94 (90)	1.55	1.42	1.74
C. K.	1.70 (99)	1.26	1.31	1.47
S. J.	1.93 (94)	1.24	1.21	1.48
Mean	2.15 (93.3)	1.41	1.38	1.83
SD	0.59 (5.36)	0.42	0.49	0.58

Group 2 (fenoterol—10 min—placebo)				
Patient	Basal FEV ₁ (%)	LAR	After fenoterol	After placebo
V. L.	1.90 (94)	1.35	1.65	1.68
L. K.	1.89 (86)	1.00	1.14	1.14
D. M. K.	3.16 (78)	2.48	3.32	3.31
C. D.	2.14 (82)	0.77	1.24	1.15
T. P.	4.52 (105)	3.03	4.52	4.75
S. A.	1.83 (81)	1.39	1.65	1.96
D. P. P.	1.75 (88)	1.34	1.63	1.75
N. J.	1.57 (86)	0.82	1.21	1.18
L. F.	1.72 (79)	1.27	1.81	1.84
L. K.	4.47 (111)	3.38	4.07	4.42
Mean	2.50 (89.0)	1.68	2.22	2.32
SD	1.14 (11.15)	0.93	1.26	1.35

METHODS

Patients

Twenty young subjects with asthma (mean age, 11.8 years; range, 8.3 to 20.6 years) were recruited from the outpatient clinic from the Department of Immunology at the University of Antwerp. All subjects suffered from moderate to severe perennial asthma, and all subjects were allergic to *Dpt*, as confirmed by the positivity of both specific IgE determination (RAST) and prick test. Their mean basal FEV₁ was 91.2% of predicted normal (range, 78% to 111%), and all subjects were able to stop antiasthmatic drugs before the allergen challenge. Informed consent was obtained from all patients or from their parents.

Bronchial provocation test with *Dpt*

In all patients, allergen challenge was performed with a standardized procedure as described earlier.¹¹ Briefly, all patients had stopped inhaled corticosteroids, theophylline, or disodium cromoglycate for 48 hours and inhaled β -

agonists for 24 hours before the first challenge day. None of the children used systemic corticosteroids or antihistamines. Challenge was performed if the subject's resting FEV₁ and vital capacity exceeded 70% of predicted normal and if the subject had been free of respiratory infection for at least 3 weeks. Two bronchial challenges, performed on 2 consecutive days, were started between 8 and 9 AM. On the first day (control day), a histamine challenge was performed as previously described,¹² and lung function was repeated at 1, 4, 6, and 8 hours. The second day was the allergen-inhalation day. The subjects inhaled through a mouthpiece and with the nose occluded; solutions were delivered by a Bird Mark 7 respirator with nebulizer (Bird Products Corp., Palm Springs, Calif.) (particle size, 0.5 to 5 μ m, according to the manufacturer) at an approximate mean flow of 0.9 L/sec.

Buffer solution was first nebulized for 1 minute as a control. Progressive dilutions (10, 100, 500, and 1000 BU/ml) of a commercial allergen extract of *Dpt* (Haarlem

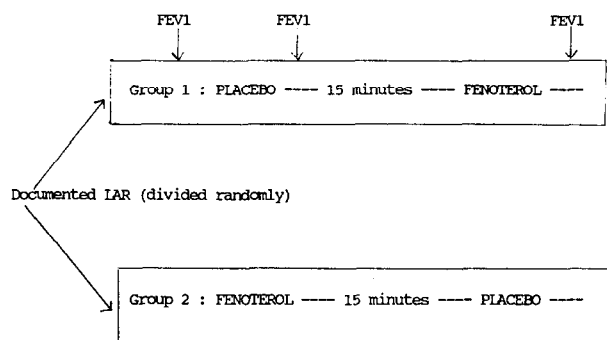


FIG. 1. Study design.

Allergen Laboratories, HAL, Haarlem, The Netherlands) were inhaled during 1 minute, starting at a dilution 100 times less (10 BU/ml) than the skin test concentration.

Bronchial responses were measured by serial monitoring of FEV₁ and vital capacity by a dry spirometer immediately and 10 minutes after each inhalation procedure. If the decrease of FEV₁ was <20% (compared with the postbuffer control) after inhalation of 1000 BU/ml, no further challenge was performed, and the subject was considered as having no IAR. After finishing the procedure for measuring the IAR, the FEV₁ was recorded at 1, 4, 6, and 8 hours, or until a significant LAR occurred. An LAR was defined as a decrease of FEV₁ of at least 20% of the postbuffer value in the observation period starting from 4 hours after the beginning of the challenge.

Study design (Fig. 1)

This study was performed as part of another study in which the occurrence of the LAR was investigated in young subjects with asthma with allergy to *Dpt*.¹¹ In the present study, the patients were included if an LAR occurred after allergen challenge and if no significant drop of FEV₁ could be detected on the control day.

The patients were randomly divided into two groups to receive double-blind: *group 1*, two puffs of placebo, and after 15 minutes, two puffs of fenoterol (400 µg); *group 2*, two puffs of fenoterol (400 µg), and after 15 minutes, two puffs of placebo.

As placebo, inert Freon propellant was used. Both fenoterol and placebo were administered as blinded metered-dose inhalers. All subjects were able to inhale appropriately. The study was started at the moment when an obvious LAR could be documented, that is, 4 to 6 hours after the allergen-inhalation procedure in all subjects. Subsequently, FEV₁ was measured before and 10 minutes after each administration of placebo or fenoterol. Changes in FEV₁, 10 minutes after each inhalation procedure, were compared between the two groups.

Statistical analysis

Group mean data were analyzed with the appropriate Student's *t* test (unpaired and paired data). Differences were considered significant at the 0.05 level.

RESULTS

The two groups were comparable according to age, basal FEV₁, and severity of the LAR (as expressed in fall of FEV₁). The study was started during the LAR, at a fall of FEV₁ in group 1 of $-34.5\% \pm 7.75$, and in group 2 of $-33.5\% \pm 14.58$, that is, 4 to 6 hours after the allergen-inhalation procedure.

In group 1, the administration of placebo did not change the FEV₁ ($-1.1\% \pm 5.00$), but after subsequent administration of fenoterol, the FEV₁ increased by $+20.7\% \pm 10.78$ ($p < 0.0001$). In group 2, the administration of fenoterol increased the FEV₁ by $+18.8\% \pm 8.07$ ($p = 0.002$), whereas subsequent inhalation of placebo did not change the FEV₁ significantly ($+3.1\% \pm 6.98$). Individual data of the subjects are presented in Table I.

Although the administration of fenoterol increased the FEV₁ significantly, the LAR was only partially reversed. After inhalation of fenoterol, there was a remaining mean decrease of FEV₁ of 14.9% in group 1 and of 11.2% in group 2, as compared to the prechallenge value of the FEV₁ ($p < 0.0001$).

DISCUSSION

In this study it is demonstrated that the administration of 400 µg of fenoterol, by a metered-dose inhaler, increases the FEV₁ significantly during an allergen-induced LAR. However, a remaining decrease of FEV₁, compared with the prechallenge value, could be observed after fenoterol administration, suggesting that bronchospasm is only part of the airway obstruction occurring during the LAR. A number of studies could demonstrate that β -agonists administered before the allergen challenge had no inhibitory effect on the development of the LAR.^{1, 2}

It appears reasonable to assume that when β -agonists are administered before the allergen challenge, their bronchodilating effect has resolved by the time the LAR occurs.⁶ It was demonstrated that β -agonists, deposited in the bronchi, are absorbed rapidly and, dependent on the choice of drug, peak plasma levels are reached 30 minutes to 3 hours after dosing. Terbutaline is probably more rapidly absorbed than isoprenaline or fenoterol, but comparative studies have not been performed.^{5, 13} Therefore, the effect of short-acting β -agonists on the LAR should be studied by administering them immediately before or during the LAR. To our knowledge, double-blind studies on that subject have not been performed. In contrast, when long-acting β -agonists are studied, inhibition of the LAR was observed.⁴ In the present study, it is suggested that bronchospasms form an essential part of the LAR but that other processes leading to airway

obstruction are also involved. The pathogenesis of the LAR is not completely understood, but it appears likely that the LAR is a manifestation of inflammatory events.¹⁴ The inflammation is probably initiated by mediators capable to attract inflammatory cells into the airway, which are released from mast cells as a consequence of an interaction with an allergen. The cells making up the inflammation and playing a central role in causing the airway obstruction of the LAR are not known, although the eosinophil has been implicated. During the LAR, mediators believed to originate from mast cells can be measured in plasma, suggesting a second phase of mediator release from mast cells during the LAR.¹⁵⁻¹⁷ The LAR, however, is not likely to be caused by the effects of mediator release on airway smooth muscle alone. Because of its severity and its prolonged duration, smooth muscle contraction can be speculated to be only in part responsible for the airway obstruction. Furthermore, inflammatory cells have been clearly demonstrated in bronchoalveolar lavages obtained during the LAR.¹⁸

In contrast, the present study has demonstrated additional evidence that smooth muscle contraction can be an important phenomenon during the LAR, although hypothetically, it can also be suggested that the second release of mediators from mast cells, appearing during the LAR, is prevented by β -agonists.¹⁹ But this appears unlikely, since β -agonists do not prevent the airway hyperresponsiveness associated with the LAR.¹ Furthermore, the fact that bronchodilatation occurs rapidly after inhalation, that is, within 10 minutes, favors a direct action on smooth muscle as the predominant site of action. In conclusion, this study demonstrates that β -agonists can partially reverse the LAR. Since this effect appears to be a bronchodilatation, a true reversion of the LAR (i.e., reversion of the inflammation and of the induced increased airway hyperresponsiveness) is not obtained by β -agonists. Therefore, it can be stated that β -agonists probably contribute only a masking effect without truly inhibiting the LAR.

We thank Miss C. Moonen for technical assistance during the bronchial challenges.

REFERENCES

1. Cockcroft DW, Murdock KY. Comparative effects of inhaled salbutamol, sodium cromoglycate, and beclomethasone dipropionate on allergen-induced early asthmatic responses, late asthmatic responses, and increased bronchial responsiveness to histamine. *J ALLERGY CLIN IMMUNOL* 1987;79:734-40.
2. Howarth PH, Durham SR, Lee TH, Kay AB, Church MK, Holgate ST. Influence of albuterol, cromolyn sodium, and ipratropium bromide on the airway and circulating mediator responses to allergen bronchial provocation in asthma. *Am Rev Respir Dis* 1985;132:986-92.
3. Hegardt B, Pauwels R, Vander Straeten M. Inhibitory effect of KWD 2131, terbutaline, and DSCG on the immediate and late allergen-induced bronchoconstriction. *Allergy* 1981;36:115-22.
4. Palmqvist M, Balder B, Dahllöf C, Löwhagen O, Svedmyr N. Inhibition of late asthmatic reaction by salbutamol and formoterol: a new long-acting β_2 -agonist [Abstract]. *NER Allergy Proc* 1988;9:377.
5. Tattersfield AE. Autonomic bronchodilators. In: Clark TJH, Godfrey S, eds. *Asthma*. London: Chapman and Hall, 1983:301-35.
6. Nelson HS. Beta adrenergic agonists. *Chest* 1982;82(suppl):33S-8S.
7. Mosimann B, Frey JG, Leuenberger P, Pecoud A. Effect of beta-adrenergic drugs on late allergic reactions following bronchial challenge with allergens. *J ALLERGY CLIN IMMUNOL* 1988;81:312. [Abstract].
8. Dorsch W, Baur X, Emslander HP, Fruhmans G. Zu Pathogenese und Therapie der allergeninduzierten verzögerten Bronchialobstruktion. *Prax Klin Pneumol* 1980;34:461-8.
9. Pepys J, Hutchcroft BJ. Bronchial provocation tests in etiologic diagnosis and analysis of asthma. *Am Rev Respir Dis* 1975;112:829-59.
10. O'Byrne PM, Dolovich J, Hargreave FE. Late asthmatic responses. *Am Rev Respir Dis* 1987;136:740-51.
11. Van Bever HP, Bosmans J, De Clerck LS, Stevens WJ. Modification of the late asthmatic reaction by hyposensitization in asthmatic children allergic to house dust mite (*Dermatophagoides pteronyssinus*) or grass pollen. *Allergy* 1988;43:378-85.
12. Stevens WJ, Vermeire PA. Bronchial responsiveness to histamine and allergen in patients with asthma, rhinitis, cough. *Eur J Respir Dis* 1980;61:203-12.
13. Pauwels R. Pharmacokinetics of inhaled drugs. In: Moren F, Newhouse T, Dolovich MB, eds. *Aerosols in medicine*. Amsterdam, New York, Oxford: Elsevier, 1985:219-24.
14. Blythe SA, Lemanske RF. Pulmonary late-phase reactions. *Ped Pulmonol* 1988;4:173-80.
15. Durham SR, Lee TH, Cromwell O, et al. Immunologic studies in allergen-induced late-phase asthmatic reactions. *J ALLERGY CLIN IMMUNOL* 1984;74:49-60.
16. Durham SR, Carroll M, Walsh GM, Kay AB. Leukocyte activation in allergen-induced late-phase asthmatic reactions. *N Engl J Med* 1984;311:1398-1401.
17. Carroll MP, Durham SR, Walsh GM, Kay AB. Activation of neutrophils and monocytes after allergen- and histamine-induced bronchoconstriction. *J ALLERGY CLIN IMMUNOL* 1985;75:290-6.
18. De Monchy JGR, Kauffman HF, Venge P, et al. Bronchoalveolar eosinophilia during allergen-induced late asthmatic reactions. *Am Rev Respir Dis* 1985;131:373-6.
19. Holgate ST, Kay AB. Mast cells, mediators, and asthma. *Clin Allergy* 1985;15:221-4.