

Evaluation of Protective Effect of Fenoterol in Allergen-Induced Bronchospasm

R

G. D'AMATO, M. SCHIANO, G. BALZANO, G. COCCO and G. MELILLO

Division of Pneumology and Respiratory Allergy, Hospital "A. Cardarelli", Naples, Italy

The purpose of this study was to determine the intensity and duration of the protective effect of fenoterol (200 μ g) in allergen-induced bronchospasm and to compare its effect with that of DSCG (20 mg). Twelve atopic-asthmatic patients, with ages ranging from 10 to 41 years, participated in the study. At the time of the study their symptoms were well controlled without the use of anti-asthmatic drugs and their FEV₁ was greater than 80% of predicted and did not vary by more than 10% on each study day.

The study was a double-blind cross over trial. Each drug was given separately at 1 week intervals according to an appropriate random plan. During the treatment the patients were given two puffs of metered dose aerosol and a capsule of inhalation powder. Each patient was given aerosol with test drug and placebo aerosol alternately, according to the double-blind method. The allergen was given 90 min after the administration of the drugs, and parameters of the respiratory function were controlled over a period of 6 h. Subsequently, the protective effect of 200 μ g fenoterol administered 4 h before the allergen was studied openly, and showed that fenoterol possesses a protective effect in allergen-induced bronchospasm. This effect, although slightly reduced, persists even when the allergen is administered 4 h later.

Key words: allergen-challenge; bronchial provocation tests; β_2 -agonist; fenoterol; prevention of asthma.

Accepted for publication 29 July 1982

CLINICAL ASPECTS

Fenoterol and DSCG are compounds used in the treatment of bronchial asthma. DSCG is used for its anti-allergic action; fenoterol, as β_2 -adrenoceptor stimulant, exhibits both bronchodilating and anti-allergic activities.

The present study compared the protective effect of fenoterol and DSCG on allergen-induced bronchospasm in 12 asthmatic patients. Fenoterol and DSCG treatment gave significant protection in allergen-induced asthma. The β_2 -agonist gave better initial protection. The protective effect of fenoterol persists even when allergen is administered 4 h after the drug.

Inhalation challenge procedures have been used for studies of asthma pathophysiology, pharmacology and therapeutics (1, 13, 14). Bronchial provocation tests (BPT) are used to investigate the activity of different anti-asthmatic drugs in preventing bronchial constriction (2, 6, 12, 16). These studies may be carried out by using dose-response curves derived from bronchial challenge after administration of placebo and the test drug. However, this procedure can be hazardous for the patient when

BPTs are performed with allergens, because by increasing the allergenic dose it is possible to induce severe late asthmatic reactions (5, 15). Therefore, in order to evaluate the pharmacological prevention of allergen-induced bronchial obstruction, it is necessary to study the effect of the drug by comparing its action with that of a different agent (15).

The purpose of this study was to determine the presence and duration of the protective action of fenoterol (200 μ g) in allergen-induced

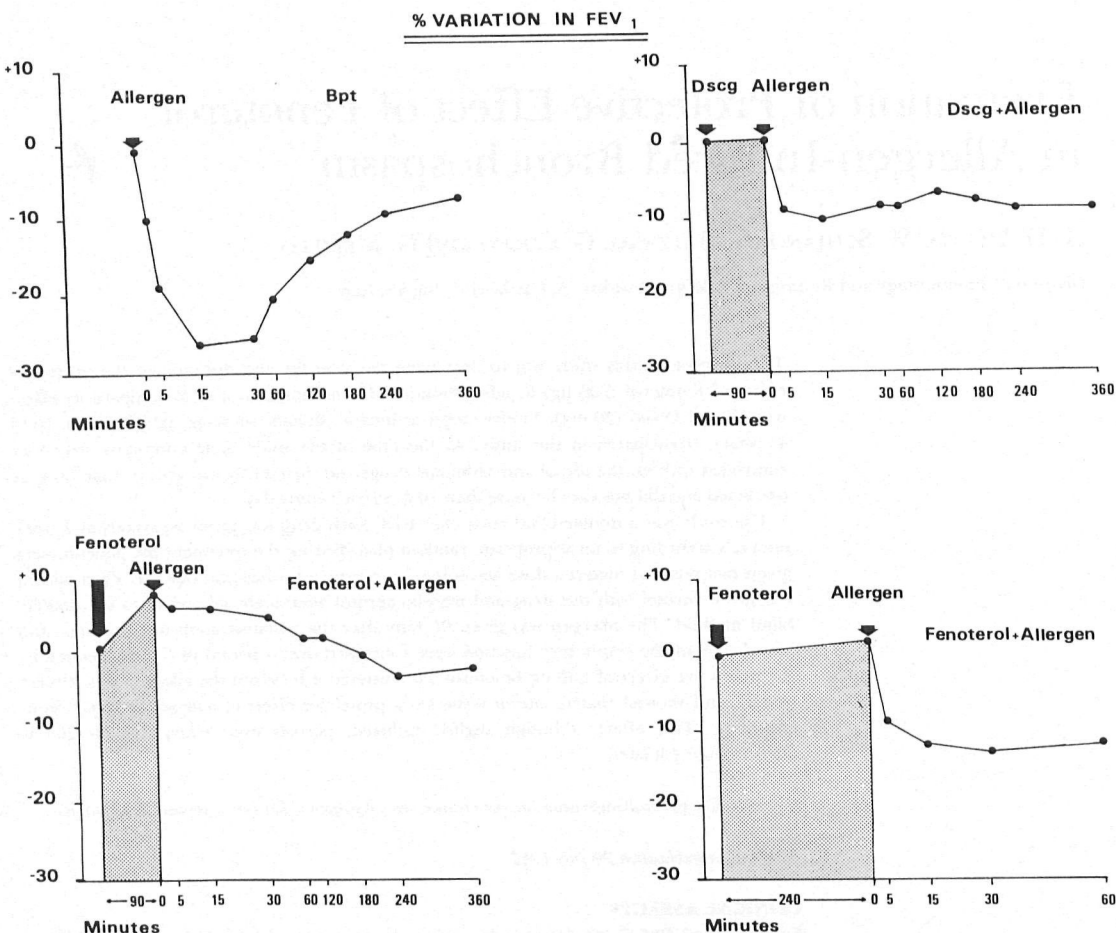


Fig. 1. Mean per cent changes in FEV₁ from the pre-challenge values for the group of 12 studied patients on each of the 4 test days. These results show: A, the decrement of FEV₁ after administration of antigen (Bpt) without premedication; B, the protective effect of DSCG (20 mg) against allergen-induced asthma; C, the bronchodilation after fenoterol inhalation (200 µg) and the protective effect of this drug against allergen-induced asthma; D, the presence of protective effect of fenoterol (200 µg) even when the allergen is administered in open trial 4 h after the drug.

bronchospasm and to compare its effect with that of disodium-cromoglycate (DSCG) (20 mg) reputedly active in preventing bronchospasm induced by allergen (12).

Fenoterol is a resorcinol derivative and is related to orciprenaline in which the *N*-substituent group is *p*-hydroxyphenylisopropyl. It is one of a series of resorcinol derivatives which are selective for beta-2-adrenoceptors (4).

MATERIAL AND METHODS

We have examined 12 subjects (6 males and 6 females) aged from 10 to 41 years; all were

atopic-asthmatic patients who reacted positively to skin tests, RAST, and BPT to *Dermatophagoides pteronyssinus*.

At the time of the study symptoms were absent in all subjects and forced expiratory volume in 1 sec (FEV₁) was greater than 80% of predicted value; baseline FEV₁ at the start of each study day varied by 10% or less. The subjects were not under specific hyposensitization. Anti-asthmatic drugs were discontinued at least 3 days before each test. Previously, various BPTs were carried out in order to select the subjects and to determine the provocation dose of specific allergen.

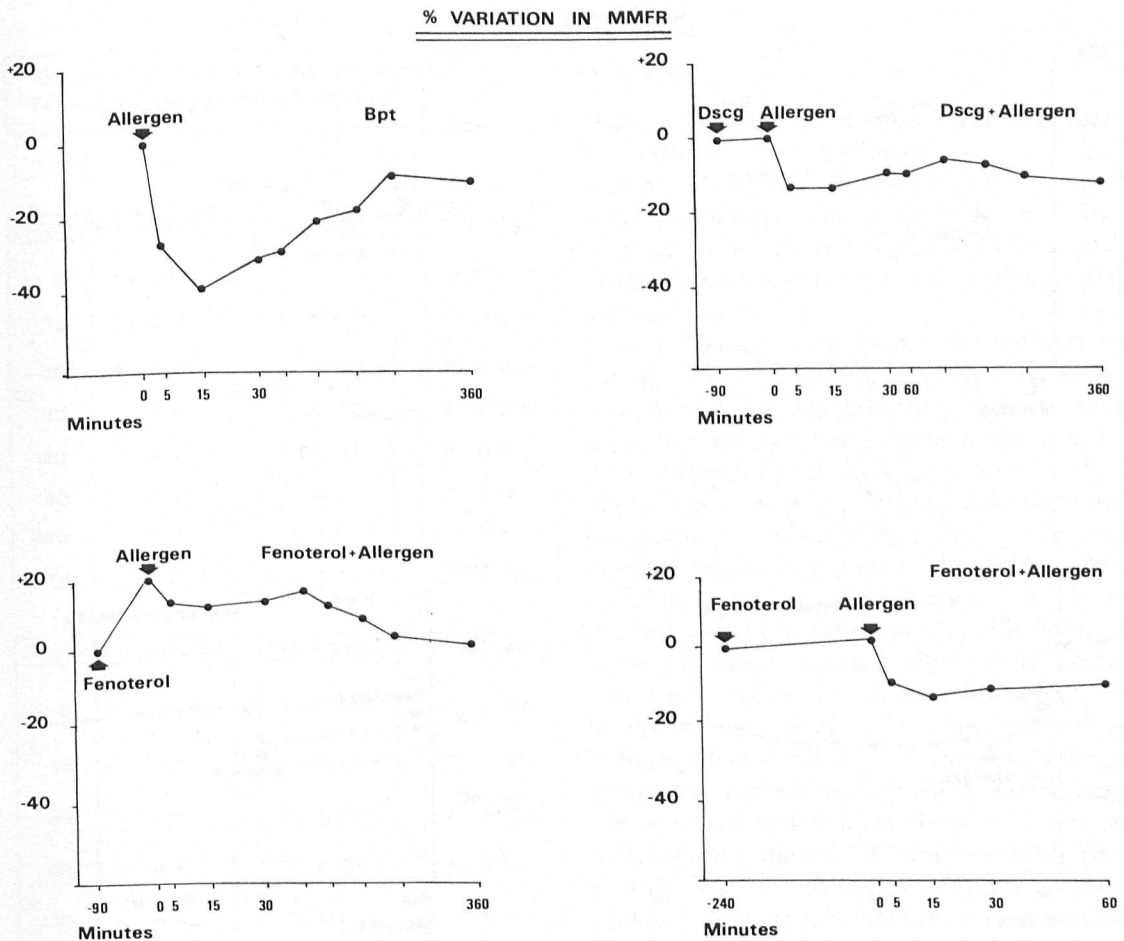


Fig. 2. Mean percentage changes in MMFR on each of the 4 test days.

The allergen, quantified in arbitrary units by RAST technique (11), was inhaled using an intermittent positive-pressure device according to our standardized method (10, 11). The provocation dose was able to determine early asthmatic responses in all 12 subjects, with a FEV_1 decrease $\geq 20\%$.

The study was a double-blind cross over trial. Each drug was given separately at 1 week intervals according to an appropriate random plan.

During the treatment the patients were given two puffs of metered dose aerosol and a capsule of inhalation powder. In accordance with double-blind method and random plan the subjects were administered alternately test drug

aerosol plus placebo powder capsule and a test drug powder capsule plus placebo aerosol. Ninety minutes after inhalation of the drugs BPT was carried out with the provocation dose of allergen previously determined.

Before the inhalation of the drugs and at fixed intervals after the administration of the allergen FEV_1 , maximal mid-expiratory flow (MMF), forced vital capacity (FVC) and oscillometric resistances (Ros) were measured.

Subsequently, in an open study, the effectiveness of fenoterol (200 μ g) in preventing allergen-induced bronchoconstriction was investigated by administering the drug 4 h before specific BPT and by measuring functional para-

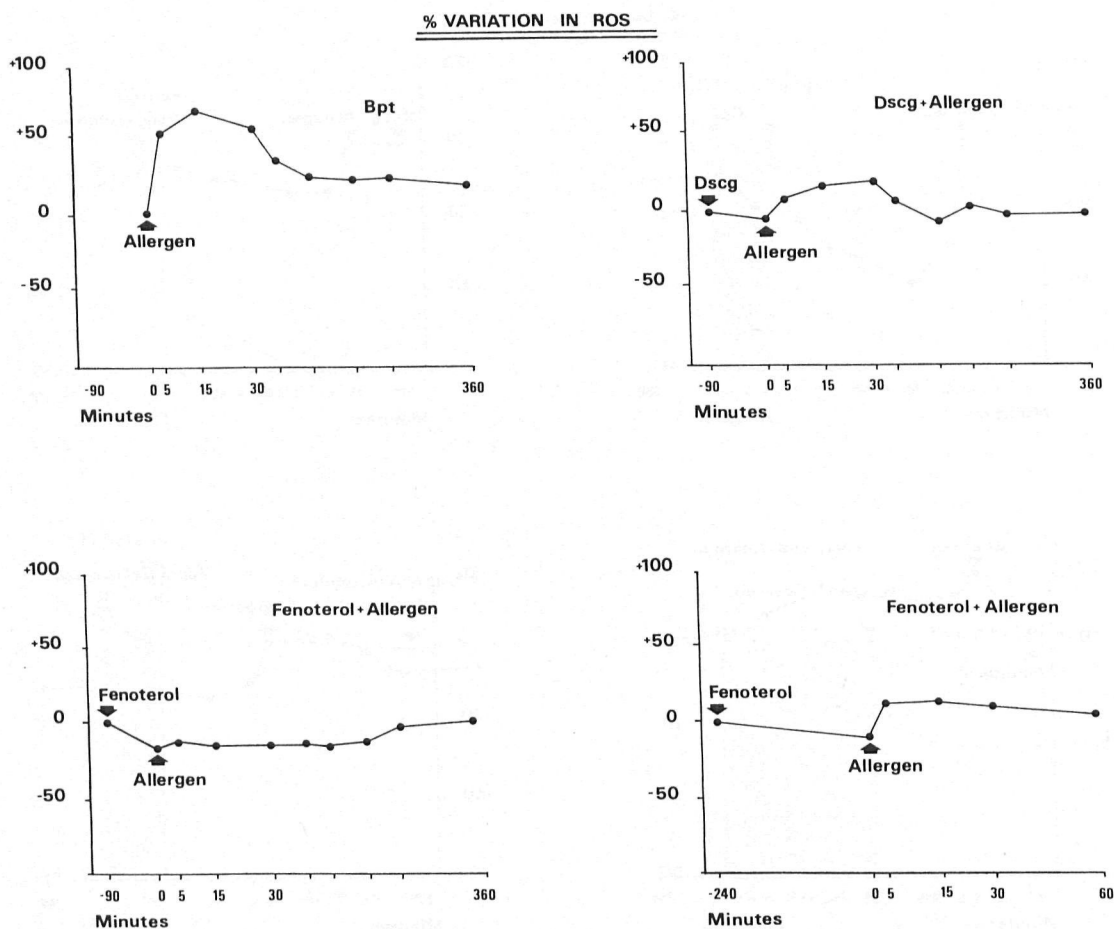


Fig. 3. Mean percentage changes in Ros on each of the 4 test days.

meters up to 60 min after allergen inhalation.

The statistical evaluation of data results has been performed according to variance analysis and to multiple comparisons.

RESULTS

A survey of the results (Figs. 1–3) clearly shows the protective effect of fenoterol and disodium-cromoglycate.

The diagrams show bronchodilation following fenoterol inhalation also in subjects with normal respiratory functions.

The results of statistical comparisons between fenoterol and disodium-cromoglycate (Table 1), show a statistically significant difference in favour of fenoterol over DSCG up to 30 min following specific BPT. After this period no statistically significant difference was found between the two drugs.

The open study, which consisted of performing BPT 4 h after the inhalation of fenoterol, showed that the protective effect of this drug, though reduced, persists even when the allergen is administered 4 h later (Figs. 1–3).

Table 1

Results of statistical comparison between
Fenoterol, Dscg and Btp (Δ absolute)

FEV₁

t. (min.)	Fen $\rightarrow$ Dscg	Fen $\rightarrow$ Bpt	Dscg $\rightarrow$ Bpt
5'	P < 0.01	P < 0.001	P < 0.001
15'	P < 0.01	P < 0.001	P < 0.001
30'	P < 0.05	P < 0.001	P < 0.001
60'	n. s.	P < 0.001	P < 0.001
120'	n. s.	P < 0.01	P < 0.01
180'	n. s.	n. s.	P < 0.05
240'	n. s.	n. s.	n. s.
360'	n. s.	n. s.	n. s.

MMFR

t. (min.)	Fen $\rightarrow$ Dscg	Fen $\rightarrow$ Bpt	Dscg $\rightarrow$ Bpt
5'	n. s.	P < 0.001	P < 0.05
15'	n. s.	P < 0.001	P < 0.001
30'	n. s.	P < 0.001	P < 0.001
60'	n. s.	P < 0.001	P < 0.01
120'	n. s.	P < 0.01	n. s.
180'	n. s.	n. s.	n. s.

ROS

t. (min.)	Fen $\rightarrow$ Dscg	Fen $\rightarrow$ Bpt	Dscg $\rightarrow$ Bpt
5'	n. s.	P < 0.001	P < 0.001
15'	n. s.	P < 0.001	P < 0.001
30'	P < 0.05	P < 0.001	P < 0.01
60'	n. s.	P < 0.001	P < 0.01
120'	n. s.	n. s.	P < 0.05
180'	n. s.	n. s.	n. s.

DISCUSSION

Protective effects of fenoterol against the allergen-induced early asthmatic response have been demonstrated by Booij-Noord et al. (3) using i.m. injected and inhaled fenoterol, and by Jorde et al. (9) and Ruffin et al. (15) who used inhaled fenoterol at doses of 400 μ g and 800 μ g, respectively.

An evaluation of the intensity of the preventive activity of fenoterol and DSCG on bronchospasm shows that the difference in results between these two drugs can be interpreted by their different pharmacological activity. It is interesting to note that 90 min after fenoterol inhalation we found a mean FEV₁ improvement of nearly 10% (Fig. 1), due to the bronchodilating activity of this drug, even when starting with FEV₁ values greater than 80% of predicted. Ninety minutes after DSCG inhalation, with a different mechanism of action, we found no increase in FEV₁. These differences in basal values at the time of allergen challenge contribute to obtaining initially a statistical result in favour of fenoterol (Table 1). Up to 30 min following specific BPT the immediate preventive effect of fenoterol on bronchospasm could be connected, in addition to the bronchodilating activity of this beta-2-adrenergic drug, probably also to its action on the inhibition of antigen-induced histamine release (7).

In the open study we administered the allergen 4 h after fenoterol inhalation to evaluate the duration of its protective activity. It has been reported in fact (8) that fenoterol is a long-acting beta₂agonist, with a bronchodilating effect lasting more than 4 h.

Manipulation of the premedication time has thus yielded information regarding the duration of activity of fenoterol. We have found that the protective effect of this drug, though reduced, is still present when the allergen is administered 4 h after inhalation of fenoterol. This protection is very likely due to a real effect of fenoterol rather than to a bronchodilation emotionally induced. In fact, according to Spector et al. (17), suggestion has a greater effect on large airways than peripheral airways and in our pa-

tients the protection was uniform in the whole respiratory tract.

REFERENCES

1. Aas, K.: The bronchial provocation test. Charles C. Thomas, Springfield, Ill., 1975.
2. Booi-Noord, H., Orié, N. G. M., Berg, W. C. & de Vries, K.: Results of provocation of human bronchial airways with allergic and non-allergic stimuli and of drug protection tests. In Orié, N. G. M. & Van der Lende, R. (eds.): *Bronchitis III*, pp. 316-330. Royal Vangorcum Ltd., Assen, 1970.
3. Booi-Noord, H., Quancier, P. H. & de Vries, K.: Protektive wirkung von berotec bei provokationstesten mit spezifischer allergen inhalation und histamin. *Int. J. Clin. Pharmacol.* 6, (Suppl. 4), 69-72, 1972.
4. Brittain, R. T., Dean, C. M. & Jack, D.: Sympathomimetic bronchodilator drugs. *Pharmacol. Ther.* 2, 423-435, 1976.
5. Cocco, G., D'Amato, G. & Melillo, G.: Non-immediate asthmatic reactions after bronchial challenge. In Melillo, G., D'Amato, G., Cocco, G. & Ceccucci, M. (eds.): *Respiratory allergy*, pp. 145-152. Masson Italia, 1980.
6. Falliers, C. J. & Katsampes, C. F.: Pharmacologic modification of induced asthma. *Ann. Allergy* 36, 99-103, 1976.
7. Fügner, A.: Inhibition of antigen-induced histamine release by beta-adrenergic stimulants in vivo. *Int. Arch. Allergy Appl. Immunol.* 54, 78-87, 1977.
8. Heel, R. C., Brogden, R. N., Speight, T. M. & Avery, G. S.: Fenoterol: a review of its pharmacological properties and therapeutic efficacy in asthma. *Drugs* 15, 3-12, 1978.
9. Jorde, W., Smidt, V., & Worth, G.: Protektive wirkung von berotec bei allergen inhalation. *Int. J. Clin. Pharmacol.* 6 (Suppl. 4), 73-74, 1972.
10. Melillo, G., Cocco, G. & D'Amato, G.: Bronchial provocation tests in etiologic diagnosis of asthma. *Bronchopneumologie* 29, 329-336, 1979.
11. Melillo, G., D'Amato, G. & Cocco, G.: Specific bronchial provocation tests. In Ricci, M., Fauci, A. S., Arcangeli, P. & Torzuoli, P. (eds.): *Developments in clinical immunology*, pp. 201-206. Academic Press, New York, 1978.
12. Pepys, J., Davies, R. J., Breslin, A. B. X., Hendrick, D. J. & Hutchcroft, B. J.: The effects of inhaled beclomethasone dipropionate (Becotide) and sodium cromoglycate on asthmatic reactions to provocation tests. *Clin. Allergy* 4, 13-21, 1974.
13. Pepys, J. & Hutchcroft, B. J.: Bronchial provocation tests in etiologic diagnosis and analysis of asthma. *Am. Rev. Respir. Dis.* 112, 829-859, 1975.
14. Rosenthal, R. R.: The emerging role of bronchoprovocation. *J. Allergy Clin. Immunol.* 64, 564-568, 1979.
15. Ruffin, R. E., Cockcroft, D. W. & Hargreave, F. E.: A comparison of the protective effect of fenoterol and Sch 1000 on allergen-induced asthma. *J. Allergy Clin. Immunol.* 61, 42-47, 1978.
16. Spector, S. L.: Use of provocation techniques for the evaluation of drug efficacy. *J. Allergy Clin. Immunol.* 64, 677-684, 1979.
17. Spector, S. L., Luparello, T. J., Kopetzky, M. T., Souhrada, J. & Kinsman, R. A.: Response of asthmatics to methacholine and suggestion. *Am. Rev. Respir. Dis.* 113, 43-50, 1976.

Address:

Dr. Gennaro D'Amato
Divisione di Pneumologia e di Allergologia Respiratoria
Ospedale "A. Cardarelli"
Naples
Italy

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.