

were negative for *Mycobacterium tuberculosis*, pyogenic organisms, and pathogenic fungi. Radiograph of the paranasal sinuses demonstrated bilateral haziness of maxillary sinuses, but a CT scan did not demonstrate any bony destruction. Intradermal challenge with antigens of *Aspergillus fumigatus* and *A. flavus* elicited strong type I and III hypersensitivity reactions. Precipitating antibodies against these antigens were also detected. The total serum IgE level was 280 IU/L (normal range, 0.0 to 14 IU/L). The patient was diagnosed as having ABPA with AAS and an operated aspergilloma.

Within 2 weeks of initiation of treatment with 30 mg of prednisolone once daily (0.5 mg/kg/day), the patient experienced a remarkable decrease in chest and nasal symptoms. Chest radiograph obtained 1 month after commencement of therapy showed a reinflated left lung (Fig. 1, B), and an ultrasonographic study did not reveal any pleural effusion.

DISCUSSION

The association of ABPA, AAS, and aspergilloma in one patient has not been documented before. Our patient, who had had asthma with eosinophilia since childhood, most probably had ABPA initially followed by aspergilloma formation in a bronchiectatic cavity. Subsequent occurrence of nasal symptoms suggests that AAS developed later. Another significant feature in our patient was the associated pleural effusion, which has been documented before in only two patients.³ The occurrence of sterile exudative pleural fluid with lymphocytic predominance, which is similar to the report of the previous two

cases, suggests that increased negative intrapleural pressure caused by collapse of the lung⁴ rather than hypersensitivity to *Aspergillus* may have been the cause. Collapse of the lung, associated pleural effusion, and ipsilateral mediastinal shift usually suggest bronchogenic carcinoma. Failure to recognize ABPA as a cause of such a clinical presentation may result in diagnostic confusion, delay in therapy, and increased morbidity.

Therapy with prednisolone produced an excellent response, which resulted in reexpansion of the left lung and resorption of the pleural fluid. Our case emphasizes that ABPA, AAS, and aspergilloma can occur in a single patient and that ABPA can mimic bronchogenic carcinoma.

We thank Mr. S. Mazumdar for photography and Mr. B. D. Sharma for secretarial assistance.

REFERENCES

1. Shah A, Khan ZU, Chaturvedi S, Ramchandran S, Randhawa HS, Jaggi OP. Allergic bronchopulmonary aspergillosis with coexistent aspergilloma: a long-term followup. *J Asthma* 1989;26:109-15.
2. Shah A, Khan ZU, Chaturvedi S, Bazaz Malik G, Randhawa HS. Concomitant allergic *Aspergillus* sinusitis and allergic bronchopulmonary aspergillosis associated with familial occurrence of allergic bronchopulmonary aspergillosis. *Ann Allergy* 1990;64:507-12.
3. Murphy D, Lane DJ. Pleural effusion in allergic bronchopulmonary aspergillosis: two case reports. *Br J Dis Chest* 1981;75:91-5.
4. Light RW. *Pleural diseases*. 2nd ed. Philadelphia: Lea & Febiger, 1990:16.

The effect of oral terfenadine on neurokinin-A-induced bronchoconstriction

N. Crimi, MD, R. Oliveri, MD, R. Polosa, MD, F. Palermo, PhD, and
A. Mistretta, MD Catania, Italy

Neuropeptides such as neurokinin A (NKA) and substance P may be implicated as inflammatory mediators in asthma because they exhibit a variety of

From Istituto Malattie dell'Apparato Respiratorio, Università di Catania, Catania, Italy.

Reprint requests: Prof. N. Crimi, MD, Via Passo Gravinia 187, 95125 Catania, Italy.

J ALLERGY CLIN IMMUNOL 1993;91:1096-8

Copyright © 1993 by Mosby-Year Book, Inc.

0091-6749/93 \$1.00 + .10 1/54/45212

Abbreviations used

NKA: Neurokinin A

FEV₁: Forced expiratory volume in 1 second

PD₁₅: Provocative dose causing a 20% fall in FEV₁

PD₂₀: Provocative dose causing a 15% fall in FEV₁

features, which may all be relevant in the pathophysiology of bronchial asthma and in the potency of bronchoconstrictors when inhaled by asthmatic subjects.¹

TABLE I. Effects of terfenadine and placebo on PD₂₀ histamine (mg) and on PD₁₅ NKA (μg) values

	Histamine study days			NKA study days		
	Baseline	Placebo	Terfenadine	Baseline	Placebo	Terfenadine
Subject No.						
1	0.05	0.05	2.04	1.93	1.67	1.59
2	0.05	0.05	0.98	2.08	2.49	0.97
3	0.03	0.08	2.02	0.67	0.77	0.55
4	0.05	0.06	0.63	0.61	0.47	0.48
5	0.03	0.03	1.21	0.66	0.66	0.66
6	0.04	0.04	0.93	0.69	0.74	0.68
Geometric mean	0.05	0.05	1.19	0.95	0.94	0.75
Range	0.03-0.05	0.03-0.08	0.63-2.04	0.61-2.08	0.47-2.49	0.48-1.59

Recent work supports the view that mediator secretion from mast cells may contribute to the airway response induced by NKA in asthma.^{2, 3} To investigate this possibility we have assessed the relative contribution of mast cell histamine to the mechanism of NKA-induced bronchoconstriction in asthma by undertaking a placebo-controlled, double-blind, randomized study with terfenadine as a potent antihistamine.

Six subjects with atopic asthma who were non-smokers with a mean ($\pm$ SEM) age of 30.7 years ($\pm$ 4.3 years) participated in the study. None had received oral or inhaled corticosteroids, theophylline, antihistamines, or cromolyn sodium within the previous month. Inhaled bronchodilators were withheld for at least 24 hours before each visit to the laboratory. The study consisted of two phases. In the first phase, in the absence of any drug treatment, subjects attended the laboratory on two separate occasions, at least 72 hours apart, to undertake dose-response studies with inhaled histamine (BDH Chemicals, Poole, Dorset, U.K.) and NKA (Peninsula Laboratories, Belmont, Calif.), respectively. Provided that forced expiratory volume in 1 second (FEV₁) did not fall by more than 10% of the baseline value, a bronchial provocation study was carried out with inhaled histamine or NKA. FEV₁ was recorded at 1 and 3 minutes after administration of each dose of agonist, and increasing doubling doses of histamine (range, 0.015 to 4 mg) or NKA (range, 0.45 to 10.44 μg) were inhaled at 5-minute intervals until FEV₁ had fallen by more than 15% (for NKA) and by >20% (for histamine) of the baseline post-saline value so that their respective PD₁₅ and PD₂₀ values could be derived. In the second phase of the study, subjects attended on four further occasions, at least 5 days apart, to undertake dose-response studies with inhaled histamine and NKA. On the first two occasions increasing doubling doses of histamine were administered after 3 days of treatment with either orally administered terfenadine (180 mg/day) or matched placebo, administered in a randomized,

double-blind fashion. On the final two occasions, subjects underwent dose-response studies with inhaled NKA after 3 days treatment with either orally administered terfenadine (180 mg/day) or matched placebo administered in a randomized, double-blind fashion. The PD₁₅ and PD₂₀ values were logarithmically transformed before comparison by Student's *t* test for paired data.

There were no significant differences in the mean baseline and postdiluent values of FEV₁ between and within study days. For the six subjects studied, the geometric mean (range) PD₂₀ and PD₁₅ values obtained on the open study days for histamine and NKA were 0.04 mg (0.03 to 0.05 mg) and 0.95 μg (0.61 to 2.08 μg), respectively. For the six subjects studied, the geometric mean (range) PD₂₀ histamine and PD₁₅ NKA values after placebo administration were 0.05 mg (0.03 to 0.08 mg) and 0.94 mg (0.47 to 2.49 μg), respectively (Table I). When compared with placebo, orally administered terfenadine produced displacement to the right of the dose-response curves obtained with histamine but not with NKA. The geometric mean (range) PD₂₀ and PD₁₅ values obtained with histamine and NKA after terfenadine administration were 1.19 mg (0.63 to 2.04 mg) and 0.75 μg (0.48 to 1.59 μg), respectively (Table I).

This study demonstrates that NKA administered by inhalation to subjects with asthma causes dose-related bronchoconstriction, which confirms the findings of previous studies with this agonist.^{4, 5} In addition, we have shown that premedication with the selective H₁-histamine receptor antagonist, terfenadine, failed to produce a significant protection for the airways against NKA-provoked decreases in FEV₁, which suggests that histamine is not involved in mediating the response with this agonist. Terfenadine was chosen as a histamine H₁ receptor antagonist because of its demonstrated potency and specificity.

The mode of action of NKA in provoking bronchoconstriction in subjects with asthma is unknown,

but possibilities include a direct effect on airway smooth muscle, an interaction with neural reflexes of both the vagal cholinergic and C-fiber afferent types, mast cell mediator release and vascular changes in the airways.¹ In human studies nedocromil sodium produced significant inhibition of decreases in pulmonary function provoked by NKA,^{4,5} which suggests that this peptide may indirectly act via an interaction on nerves and/or inflammatory cells.

A recent study by Lowman et al.² has demonstrated that NKA can provoke release of histamine from human skin mast cells *in vitro*. That the same mechanism of action may be active at the airways level is supported by a recent investigation carried out in the rat, in which histamine is present in large amount in bronchoalveolar lavage fluid recovered after NKA infusion.³ Our failure to show a significant inhibitory effect of orally administered terfenadine on the airway response to challenge with inhaled NKA is in accordance with what has been demonstrated in a recent study of subjects with rhinitis, which failed to demonstrate histamine release in lavage fluid after nasal challenge with NKA.⁶ In a similarly designed clinical trial, we have also shown that premedication with the potent histamine H₁ receptor antagonist astemizole failed to protect against substance-P-induced bronchoconstriction,⁷ which supports our view that endogenously released histamine does not contribute as

mediator of neuropeptide-induced bronchoconstriction in human asthma.

In conclusion, we have shown that terfenadine failed to produce a significant protection of the airways against provocation with NKA and that it is unlikely that mast cell histamine release contributes to the action of this peptide in asthmatic airways.

REFERENCES

1. Barnes PJ, Baraniuk JN, Belvisi MG. Neuropeptides in the respiratory tract. *Am Rev Respir Dis* 1991;144:1187-98.
2. Lowman MA, Benyon RC, Church MK. Characterization of neuropeptide-induced histamine release from human dispersed skin mast cells. *Br J Pharmacol* 1988;95:121-30.
3. Pauwels R, Joos G, Kips J, Van Der Straeten M. Adenosine and neurokinin A cause histamine release in the airways [Abstract]. *Am Rev Respir Dis* 1988;137:A212.
4. Joos GF, Pauwels RA, van der Straeten ME. The effect of nedocromil sodium on the bronchoconstrictor effect of NKA in subjects with asthma. *J ALLERGY IMMUNOL* 1989;83:663-8.
5. Crimi N, Palermo F, Oliveri R, Palermo B, Polosa R, Mistretta A. Protection of nedocromil sodium on bronchoconstriction induced by inhaled NKA in asthmatic patients. *Clin Exp Allergy* 1992;22:75-81.
6. Braunstein G, Fajac I, Lacronique J, Frossard N. Clinical and inflammatory responses to exogenous tachykinins in allergic rhinitis. *Am Rev Respir Dis* 1991;144:630-5.
7. Crimi N, Palermo F, Oliveri R, et al. Influence of antihistamine (Astemizole) and anticholinergic drugs (Ipratropium bromide) on bronchoconstriction induced by SP. *Ann Allergy* 1990; 65:115-20.

ANNOUNCEMENT

AMERICAN BOARD OF ALLERGY AND IMMUNOLOGY

A Conjoint Board of the
American Board of Internal Medicine and the American Board of
Pediatrics is pleased to announce its

1993 ABAI CERTIFICATION PROCESS

Monday, Oct. 11, 1993

Washington, D.C., and Denver, Colo.

Registration: through March 31, 1993

Completed applications must be postmarked by March 31, 1993, to avoid a late, nonrefundable penalty fee. No applications will be accepted after August 15, 1993.

Please address all requests to Herbert C. Mansmann, Jr., MD, American Board of Allergy and Immunology, 3624 Market St., Philadelphia, PA 19104-2675; phone 215/349-9466. FAX 215/222-8669.

Recertification is available to ABAI Diplomates via and Alternative Pathway of the 1993 Certification Process. Inquiries should be directed as noted.