

Sputum E-cadherin and asthma severity

To the Editor:

Animal studies suggest that airway inflammation might decrease E-cadherin in the epithelium, and loss of E-cadherin might play a role in the damage of the airway epithelium seen in patients with asthma.^{1,2} We examined soluble E-cadherin (sE-cadherin)³ in induced sputum of asthmatic subjects and determined the relationship between airway epithelial damage and asthma severity.

We studied 15 control subjects and 44 asthmatic subjects. Age of onset of asthma was determined by the subjects' own report of their age at the time of initial physician diagnosis of asthma or onset of symptoms, whichever occurred earlier. Duration of asthma was calculated from the age of onset.

Asthma severity was assessed according to the recommendations for classification of asthma severity of the National Heart, Lung, and Blood Institute/World Health Organization Workshop on the Global Strategy for Asthma,⁴ which was modified to classify the patients into 3 categories: those with intermittent asthma, those with mild-to-moderate persistent asthma, and those with severe persistent asthma.⁵ Patients with intermittent asthma ($n = 8$) had increased airway hyperresponsiveness, as defined by a PC_{20} value of less than 8 mg/mL, the presence of less than 1 episodic symptom per week, and a history of using less than 1 dose of inhaled short-acting β_2 -agonist per week. None had nighttime asthma. Their FEV_1 values were greater than 80% of predicted value, with peak expiratory flow (PEF) diurnal variation of less than 20%. Patients with mild-to-moderate persistent asthma ($n = 23$) had daytime symptoms at least once a week to several times daily, nighttime asthma greater than 2 times a month, and history of using inhaled short-acting β_2 -agonists at least once a week. Their FEV_1 values were greater than 60% of predicted value, and PEF diurnal variation was less than 30%. Patients with severe persistent asthma ($n = 13$) had frequent symptoms limiting their activities, with attacks every night and frequent exacerbations. They had either FEV_1 values of less than 60% of predicted value or PEF diurnal variation of greater than 30%. Patients with mild-to-moderate asthma were treated with 400 μ g of beclomethasone dipropionate or 200 μ g of fluticasone propionate. Patients with severe asthma were treated with 800 μ g of beclomethasone dipropionate or 400 μ g of fluticasone propionate, receiving 5 to 10 mg/d regular oral prednisolone.

Soluble E-cadherin in sputum, induced by means of hypertonic saline solution,⁶ was measured with a sandwich ELISA kit according to the manufacturer's method (TAKARA Biochemicals Co, Osaka, Japan). The detection limit for this kit when using a concentration procedure was 12.5 ng/mL. Data are expressed as nanograms per milliliter in original sputum.

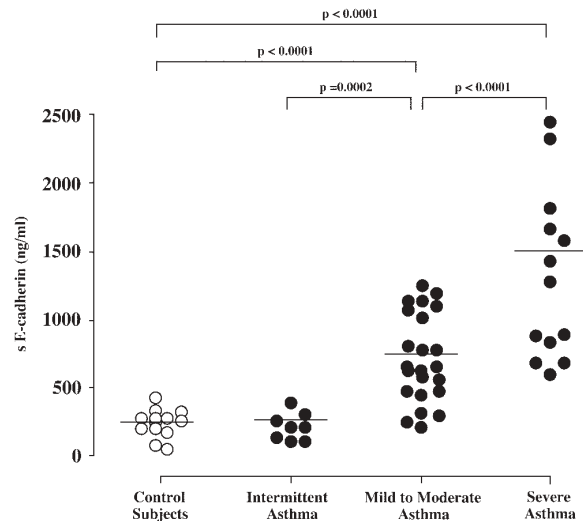


FIG 1. Soluble E-cadherin (sE-cadherin) levels in induced sputum of asthmatic and control subjects.

Fig 1 shows the sE-cadherin levels in sputum in control and asthmatic subjects. Patients with mild-to-moderate and severe asthma had higher sputum sE-cadherin levels than control subjects, with a progressive increase that was related to asthma severity. In asthmatic subjects sE-cadherin was inversely correlated with FEV_1 ($r = 0.43$, $P < .01$) and was correlated with duration of asthma ($r = 0.61$, $P < .001$). However, the use of glucocorticosteroids did not change the level of sputum sE-cadherin.

In the present study sputum sE-cadherin levels reflect clinical activity of asthma, regardless of treatment, such as the use of glucocorticosteroids. In addition, sputum sE-cadherin correlated with decreases in FEV_1 and duration of asthma. Therefore the relationship between sputum sE-cadherin levels and asthma severity might indicate persistent epithelial damage in symptomatic asthma.

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Heterogeneity of IgE response to cefteram pivoxil was noted in 2 patients with cefteram-induced occupational asthma

To the Editor:

Cephalosporins are known to cause occupational asthma, and few reports show that the pathogenesis might be IgE mediated.^{1,2} Although high-molecular-weight occupational allergens elicit hypersensitivity reactions that are well understood, the pathogenesis of occupational asthma induced by low-molecular-weight chemical agents is unclear. Drugs of low molecular weight might act as haptens and combine with a protein to elicit an immunologic response. To date, there has been no report showing serum-specific IgE to cephalosporins. This is the first report to detect specific IgE binding to cefteram pivoxil (Tomiron) and to compare IgE responses caused by cefteram in 2 asthmatic patients.

In this report we describe the findings of 2 patients with cefteram-induced occupational asthma who had worked in a pharmaceutical company. Skin prick tests and bronchial provocation tests with cefteram were performed to compare IgE responses. The patients were exposed to cefteram until 2 days before evaluation. Cefteram-human serum albumin (HSA) conjugates prepared in our laboratory according to the methods of Rose et al³ were used to detect serum-specific IgE to cefteram by means of ELISA. For ELISA inhibition tests, sera were preincubated with cefteram alone, HSA alone, and cefteram-HSA conjugate and then subjected to IgE ELISA. Patients 1 and 2 had an allergen/histamine ratio (the ratio of the size of the wheal caused by allergen and histamine) of 1 and 3, respectively, to cefteram on skin prick testing. Patient 1 was nonatopic, patient 2 had positive responses to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, and neither patient had a previous history of drug allergies. Both exhibited early asthmatic responses after inhalation of cefteram powder solution. The PD₂₀ values were 2.12 and 1.98 mg for patients 1 and 2, respectively. Both patients had high levels of serum-specific IgE to cefteram-HSA conjugate (0.39 and 1.5 O.D. value) when the positive cutoff value was determined as mean $\pm$ 3 SD. However, ELISA inhibition tests revealed 2 different patterns. Patient 1 showed marked inhibition patterns to both cefteram alone and cefteram-HSA conjugate, with minimal inhibitions to house dust mite and HSA alone (Fig 1), whereas in patient

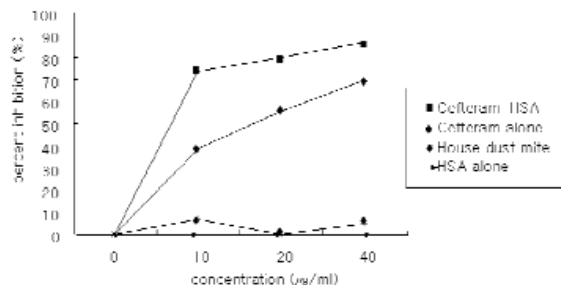


FIG 1. Percentage inhibition of cefteram-IgE ELISA with serial additions of cefteram-HSA conjugate, cefteram alone, house dust mite, and HSA alone in patient 1.

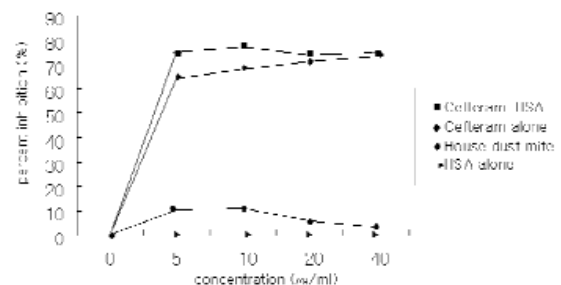


FIG 2. Percentage inhibition of cefteram-IgE ELISA with serial additions of cefteram-HSA conjugate, cefteram alone, house dust mite, and HSA alone in patient 2.

2 marked inhibitions to cefteram-HSA conjugate were noted, but lesser (half) inhibitions to cefteram alone, house dust mite, and HSA alone were seen (Fig 2).

These results suggest that different IgE responses to cefteram might have developed against haptens, new antigenic determinants (NADs), or both. In a study on isocyanate chemicals, it was suggested that immune responses could involve both carrier and hapten.⁴ The antigenic determinants might be formed by the interactions of the chemical hapten and autologous proteins. In this study ELISA inhibition suggests that IgE antibody developed against hapten in patient 1, whereas in patient 2 the IgE response developed mainly against NADs and, in part, hapten. This study demonstrates that IgE responses to cefteram might involve both haptens and NADs and could be different between sensitized individuals.

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