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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

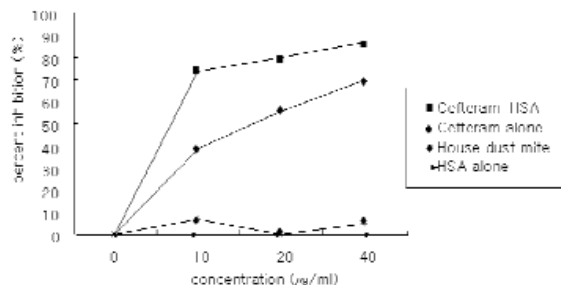


FIG 1. Percentage inhibition of cefteram-IgE ELISA with serial additions of cefteram-HSA conjugate, cefteram alone, house dust mite, and HSA alone in patient 1.

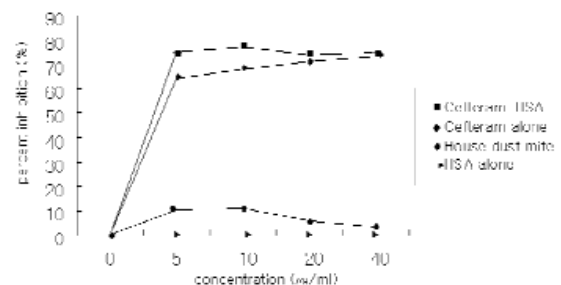


FIG 2. Percentage inhibition of cefteram-IgE ELISA with serial additions of cefteram-HSA conjugate, cefteram alone, house dust mite, and HSA alone in patient 2.

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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No difference in type 1 T-cell immune responses to human cytomegalovirus antigens between atopic children and nonatopic children

To the Editor:

The relationship between atopic phenotypes and T-cell function is not fully understood. The classic atopic manifestations, such as atopic dermatitis, bronchial asthma, and seasonal allergic rhinoconjunctivitis, are characterized by an increased IgE synthesis and a T_H2 -dominated immune response.¹

Viral infections are known to have a strong influence on the human immune system. Infections with human cytomegalovirus (HCMV) have a high prevalence and are lifelong. The infection is greatly dependent on type-1 cytokine secreting and cytotoxic T cells. Almost all HCMV-seropositive individuals express a type 1 T-cell response to HCMV.²

The structural phosphoprotein UL83 (pp65) and the nonstructural protein IE-1 are major targets of the $CD8^+$ T-cell response³; they were therefore selected for the present study. HCMV-pp65/IE-1-specific $CD8^+$ T cells account for more than 1% of our peripheral blood T cells.⁴ Specific stimulation of these $CD8^+$ T-cell subsets might therefore reflect $CD8^+$ T-cell reactivity.

Type 1 $CD4^+$ or $CD8^+$ cells produce key cytokines, such as IFN- γ , TNF- α , and GM-CSF, whereas type 2 T cells are characterized predominantly by secretion of IL-4, IL-5, and IL-13. Whereas type-2 T cells promote IgE production and eosinophilia, type 1 T cells induce cytotoxic and delayed-type hypersensitivity responses, stimulate secretion of complement-fixing antibodies (IgG1,3), and suppress the T_H2 function. Cytotoxic T lymphocytes eliminate virus-infected cells. Type 1 cytokines—in particular, IFN- γ —inhibit viral promoter activity and replication. A strong type 1 T-cell response suppresses type 2 responses and protects against atopic disease, at least in atopic dermatitis.⁵

More than 60% of adults in the industrial nations are HCMV-seropositive. Through use of highly sensitive PCR techniques, HCMV DNA is also detectable in at least 50% of seronegative blood donors,⁶ suggesting a high prevalence of HCMV exposure. The HCMV genome contains more than 200 open reading frames, possibly coding for as many proteins. An infection with HCMV leads to a strong T_H1 -type cytokine secretion pattern.

We evaluated whether atopic subjects characterized by a T_H2 -cytokine secretion pattern respond differently to T_H1 -inducing viral antigens in vitro. We used flow cytometry to analyze the HCMV-specific T-cell responses of children with and children without atopic disease.

Twenty-four atopic children were selected on the basis of a clinical diagnosis of asthma, allergic rhinoconjunctivitis and/or atopic dermatitis plus allergic sensitization (atopic dermatitis, $n = 9/24$; bronchial asthma, $n = 7/24$; allergic rhinoconjunctivitis, $n = 9/24$; allergic sensitization, $n = 24/24$). The mean age was 11.8 years (range, 2-17 years); 71% of the subjects were boys and 29% were girls. Allergic sensitization was defined as sensitization to at least one of the common aeroallergens or food allergens. Total and specific serum IgE levels were measured with the in vitro immunoassay CAP system (Pharmacia Diagnostics, Freiburg, Germany). Specific sensitization was defined as ≥ 0.35 kU/L.

We compared these individuals with 76 children who did not have any atopic history or clinical signs of atopy (without asthma, allergic rhinoconjunctivitis, atopic dermatitis, and sensitization). The children were matched for age and sex. The mean age in the control group was 10.3 years (range, 1-17 years); 54% were boys and 46% were girls. Children taking immunosuppressive medications, such as oral glucocorticosteroids, were not included in the study.

IFN- γ -positive T cells were identified by flow cytometry (FACS Calibur, Becton, Dickinson and Company, San Jose, Calif) after stimulation of heparinized blood samples with inactivated HCMV lysate and pp65 and IE-1 protein-spanning peptide pools. After 1 hour of stimulation at 37°C, brefeldin A was added (2.5 μ L/mL); 16 hours later, the cells were collected. The erythrocytes were lysed by BD Lysing solution, and the cell samples were stained for CD4, CD8, CD69, and CD3 surface antigens. PMA and Ionomycin were applied as positive controls. Negative controls and isotype controls were made to detect and eliminate potential unspecific reactivity.

A detectable T_H1 immune response based on IFN- γ -positive T cells was defined as a gated event result of $\geq 0.20\%$. In addition, the humoral immune response was analyzed by measurement of HCMV-specific IgG (Immulate, DPC-Biermann, Bad Nauheim, Germany).

Statistical significance was calculated by means of χ^2 and Yates tests through use of computer software (SPSS version 8.0); a P value of $< .05$ was considered statistically significant.

The overall prevalence of HCMV seropositivity in the study population of 100 children was 40%; 60% of all children were HCMV-seronegative. A type 1 immune response with an increase in IFN- γ -positive T cells after stimulation with at least one of the HCMV stimuli was measured in 50% (20/40) of the HCMV-seropositive children and in 6.7% (4/60) of the HCMV-seronegative children. Of the total study population of 100 children, a T_H1 immune response was detected in 31.3% after antigen stimulation ($CD4^+$ only), in 19% after pp65 stimulation ($CD4^+/CD8^+$), and in 29% after IE-1 stimulation ($CD4^+/CD8^+$).

The prevalence of HCMV seropositivity in the atopic children was 50%; this compared with 37% in the nonatopic children.

Comparing atopic children versus nonatopic children with respect to T_H1 reactivity, we found a type 1 immune