

Michael Gold, MD, FRACP^c
David Gillis, FRACP, FRCPA^a
Elizabeth M. Benson, FRACP, FRCPA^b

^aImmunology Department
IMVS
Box 14
Rundle Street Post Office
Adelaide 5000
Australia

^bDepartment of Immunopathology, ICPMR
Westmead Hospital
Wentworthville, Australia

^cWomen's and Children's Hospital
North Adelaide, Australia

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Occupational asthma and IgE sensitization to 7-aminocephalosporanic acid

To the Editor:

Cephalosporins cause occupational asthma, and it has been suggested that the pathogenesis is mediated by IgE.^{1,2} 7-ACA (aminocephalosporanic acid) is a major intermediate metabolite in the synthesis of cephalosporin. There has been one published report of occupational asthma caused by 7-ACA, in which a nonimmunologic mechanism was suggested.³ Ours is the first investigation to detect serum IgE specific to 7-ACA-HSA (human serum albumin) conjugate in an exposed worker with occupational asthma.

This report describes the clinical findings in two asthmatic workers in a pharmaceutical plant who were exposed to 7-ACA powder used to synthesize ceftriaxone. To evaluate the IgE response, skin prick tests (SPTs) were performed in 5 exposed workers. To confirm bronchial sensitization in the two symptomatic workers, a methacholine bronchial challenge and specific bronchial provocation tests (BPTs) with 7-ACA and ceftriaxone were done. 7-ACA-HSA and ceftriaxone-HSA conjugates were prepared in our laboratory according to a method described previously.⁴ For IgE-ELISA, sera was incubated in 7-ACA-HSA conjugate or sham HSA coated well, and anti-human IgE and second antibody were added. Twenty nonatopic, healthy subjects with no history of exposure, who had negative SPTs to ACA and ceftriaxone, were enrolled as control subjects. Final absorbance value was determined by subtraction from that of sham HSA coated well. The positive cutoff value for specific IgE was determined by using the mean $\pm$ 3 SD of the absorbance values (patient LB). For the ELISA inhibition test, serum with high levels of specific IgE was preincubated with the free forms of 7-ACA and ceftriaxone, as well as with 7-ACA-HSA and ceftriaxone-HSA conjugates, and then subjected to IgE ELISA.

Table I summarizes the clinical features of the five exposed workers. None of the asymptomatic workers had positive responses to 7-ACA or ceftriaxone on SPT. However, two asthmatic subjects with work-related respiratory symptoms with or without rhinitis were found. Both patients had airway hyperresponsiveness to methacholine. Patient LB had a strong positive response to 7-ACA on SPT and had immediate bronchoconstriction after inhaling 7-ACA-powder solution during the specific BPT. Furthermore, high serum-specific IgE binding to 7-ACA-HSA conjugate was noted on ELISA (Fig 1, A). Patient NS had a negative response to 7-ACA on SPT but developed significant bronchoconstriction on 7-ACA BPT. Serum-specific IgE antibody was not detected. None of the workers had positive responses to ceftriaxone on specific BPT. When the IgE-ELISA inhibition test was performed by using the serum from patient LB, significant inhibition was noted in a dose-dependent manner with the serial addition of 7-ACA-HSA conjugate, whereas there was partial inhibition with free 7-ACA (Fig 1, B). Minimal inhibition was noted with free ceftriaxone, sham HSA, or ceftriaxone-HSA conjugate.

The pathogenesis of occupational asthma induced by low-molecular-weight drugs requires further study. These drugs may act as haptens and combine with a protein to elicit an immunologic response. In this study, we can suggest two different pathogenic mechanisms leading to occupational asthma caused by 7-ACA. In patient LB, an IgE-mediated mechanism was the major mechanism, as he showed positive responses on SPT and BPT to 7-ACA and had high serum levels of IgE specific to 7-ACA-HSA conjugate. By contrast, although patient NS clearly had work-related asthma symptoms and a positive response to 7-ACA on BPT, serum-specific IgE was undetectable,

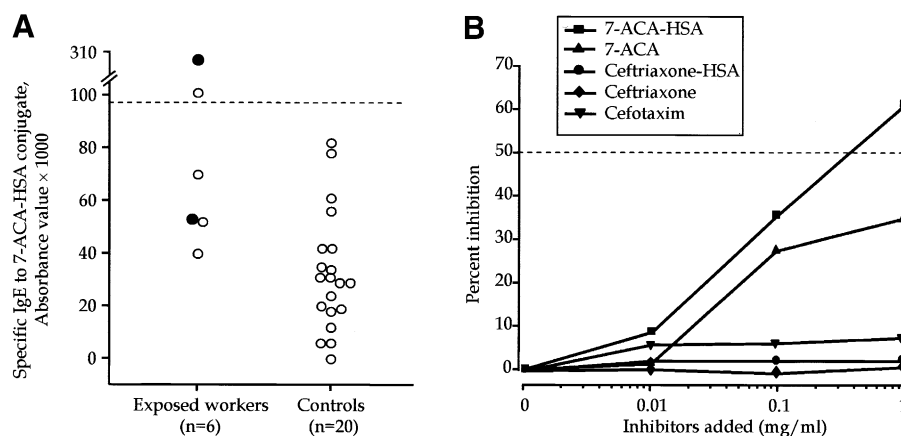


Fig 1. A, Specific IgE bindings to 7-ACA-HSA conjugate by ELISA in exposed workers and control subjects. Closed circle, symptomatic workers; open circle, asymptomatic subjects. Dotted line indicates positive cutoff value. B, Percent inhibition of IgE-ELISA to 7-ACA-HSA conjugate with additions of 7-ACA and ceftiraxone-HSA conjugates and 7-ACA or ceftiraxone alone.

TABLE I. Clinical characteristics of 5 exposed workers

Subject no.	Sex/age (y)	Exposure duration (mo)	Rhinitis	Work-related respiratory symptoms	Skin prick wheal size (mm)			Bronchoprovocation test	
					7-ACA	Ceftriaxone	mPC20	ACA	Ceftriaxone
1	M/26	26	+	+	17 $\times$ 10	14 $\times$ 8	0.39	+	—
2	M/28	27	—	+	—	—	0.19	+	—
3	M/23	13	—	—	—	—	ND	ND	ND
4	F/25	26	—	—	—	—	ND	ND	ND
5	M/27	16	—	—	—	—	ND	ND	ND

7-ACA, 7-aminoccephalosporanic acid; M, male; F, female; ND, not done; mPC20, methacholine PC20.
—, Absence; +, presence.

suggesting nonimmunologic mechanisms in the pathogenic mechanism. A previous study on cefteram pivoxil-induced asthma suggested that IgE responses involve both the carrier protein and hapten,⁴ which may differ between sensitized individuals. New antigenic determinants of the 7-ACA conjugate may form as a result of interactions between the hapten and autologous proteins. The ELISA inhibition test result suggests that the IgE responses to 7-ACA-HSA conjugate may develop mainly against a new antigenic determinant and, in part, against the hapten.

Moreover, patient LB was also sensitized to ceftiraxone but showed negative responses to the ceftiraxone-BPT. The ELISA study revealed one asymptomatic worker sensitized to 7-ACA. Further investigation is needed to evaluate the clinical significance of this asymptomatic sensitized worker.

In conclusion, we described two patients with occupational asthma caused by 7-ACA. Both IgE-mediated and nonimmunologic mechanisms were noted.

Hae-Sim Park, MD^a
Ki-Up Kim, MD^b

Young-Mok Lee, MD^b
Jeong-Hee Choi, MD^a
June-Hyuk Lee, MD^b
Sung-Woo Park, MD^b
An-Soo Jang, MD^b
Choon-Sik Park, MD^b
^aAjou University School of Medicine
Suwon, Korea
^bAsthma Genome Research Group
Soonchunhyang University Hospital
Bucheon, Korea

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