

Correspondence

Cephalosporin allergens: Is the cephalosporoyl and R1 side-chain focus too narrow?

To the Editor:

Since the early chemical and clinical structure-activity work on penicillin allergens, there has been a dearth of chemically based, characterized drug allergen studies. In particular, the lack of insights into precise cephalosporin allergenic determinant structures is in contrast to the advances shown with their β -lactam relatives. With respect to both these issues, the letter from the laboratory of Pérez-Inestrosa is an important and welcome contribution to cephalosporin drug allergy research and ultimately clinical practice.¹ In 2001, Venemalm² showed that α -aminocephalosporins such as cefaclor and cephalexin undergo aminolysis with formation of a pyrazinone degradation product that, as a conjugate with polylysine, bound IgE antibodies in sera from 9 patients with suspected β -lactam allergies. Demonstration of the intramolecular cyclization and oxidation mechanism leading to formation of the pyrazinone derivative, its synthesis, and immunologic evaluation¹ now potentially offers a useful characterized allergenic structure for *in vitro* and skin test diagnoses of aminocephalosporin-allergic recognition.

Despite the instability and fragmentation of cephalosporoyl conjugates, some uncharacterized solid phases prepared after aminolysis of a number of different cephalosporins can detect cephalosporin-reactive IgE antibodies.^{3,4} A study by Romano et al.⁴ for example, involving 70 patients, showed positive results in 74% of cases with an assay specificity of 100%. The uncharacterized nature of these conjugates however does not contribute to the identification of allergenic structures detected by patients' IgE antibodies. In Martín-Serrano et al.,¹ a question arises concerning the "solid phase PLL-cefaclor" used in immunologic IgE inhibition assays. What procedures were used to preserve the integrity of the cefaclor molecule in the conjugate? Details of the conjugation of cefaclor are not provided but if conditions to prepare a cephalosporoyl conjugate were used, fragmentation of the molecule would result, leading to an unknown mix of undefined structures on the solid phase and associated uncertainties interpreting inhibition results.

Preoccupation with the well-established importance, and probable predominance, of allergic recognition of the R1 side chain in cephalosporin allergies continues. Reasons for this include the lack of appreciation of the heterogeneity of the IgE

response to drugs including cephalosporins; apparent lack of awareness of more than 1 population of anticephalosporin antibodies of different specificity in the same patient⁵; preoccupation with the aminolysis approach that leaves the R1 side chain (or parts of it) detectable; and the consequent neglect of investigative approaches designed to investigate other possible coupling positions on the dihydrothiazine ring, for example, via the carboxyl at position 4^{5,6} or the R2 side chain with, of course, the necessary accompanying stability studies of any products so formed. In addition to recognition of the whole molecule,^{5,6} a number of published observations indicate that the R1 side chain is not the sole determinant because it is not unusual to find aminocephalosporin-allergic individuals who are not allergic to other β -lactams with the same or similar side chain.^{5,7} And importantly, it should be remembered that the allergenic recognition spectra of IgE antibodies from a cephalosporin-allergic patient after injection or ingestion of an intact and undegraded cephalosporin will not necessarily match the relatively small range of specificities identified *in vitro* using chemically modified drug conjugates and degraded drug structures.

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