

Correspondence

Allergenic significance of cephalosporin side chains

To the Editor:

At the clinical level, structural similarities and differences between individual cephalosporins appear to be frequently overlooked in selecting drugs for allergy avoidance. In their study of IgE-mediated hypersensitivity to cephalosporins, Romano et al¹ rightly draw attention to the need to consider structural features in addition to skin and provocation test results when selecting alternative cephalosporins. From their assembled data showing the many reaction patterns detected, and in the absence of any significant adjunct testing (only 8 patients had

IgE antibodies to cefaclor, the only specificity tested), attempts are made to interpret the findings in terms of likely R1 side-chain structures, especially the presence of the methoxyimino group found on a number of third- and fourth-generation cephalosporins. Possible recognition of R2 side chains is suggested for 1 patient. There is ample evidence that the R1 side chains of cephalosporins can be involved in allergic recognition,^{2,3} and current thinking seems to be that it is the predominant, if not the only, allergenic structure on cephalosporins. This conclusion appears to have been influenced by the known lability of the dihydrothiazine ring; clear allergenic involvement of the aminobenzyl R1 group in some allergic patients; the lack of testing (especially *in vitro*) aimed at detecting

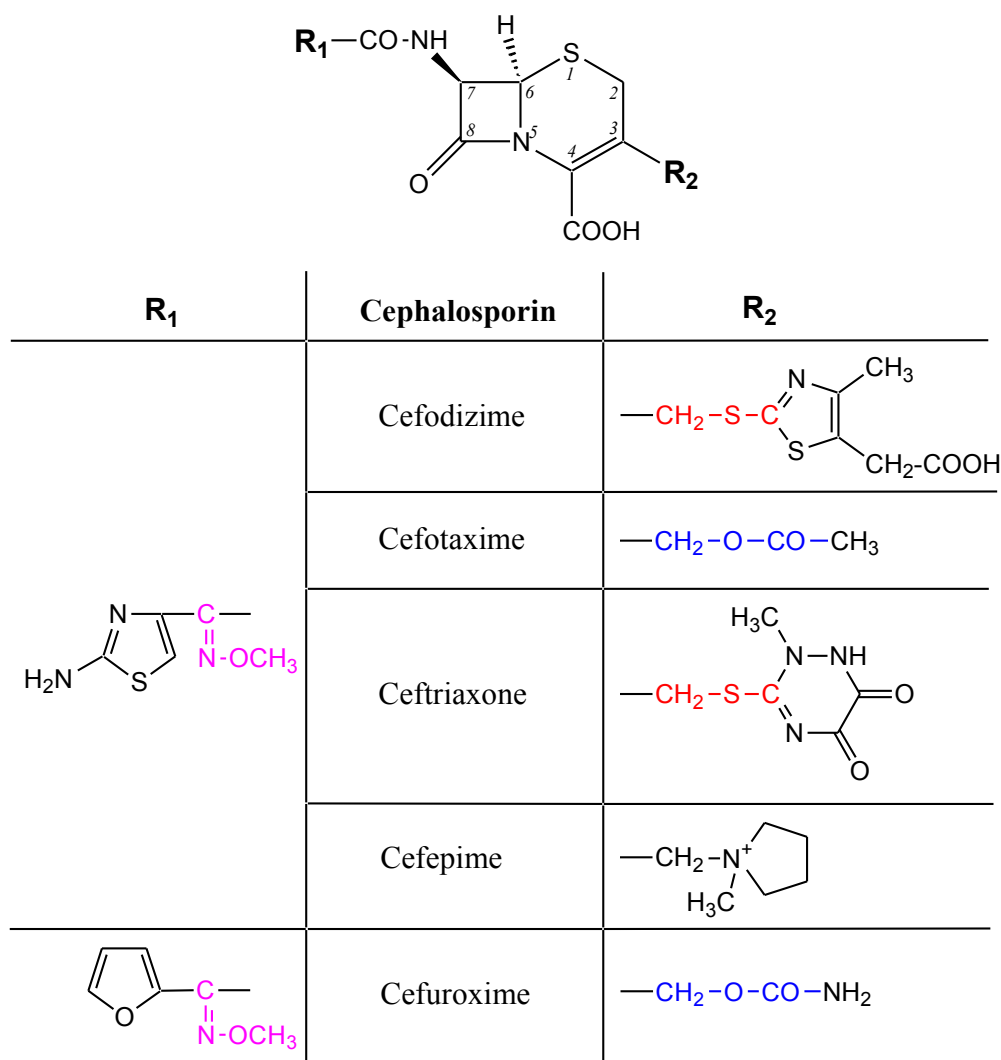


FIG 1. General structure of cephalosporins and structures of cephalosporins used in the study¹ showing the R1 methoxyimino group (magenta) and the R2 ester and thioether groups (blue and red, respectively). Space-filling models show that, compared with cefodizime, the thioether group of ceftriaxone is at least partially hindered by the adjacent ring *N*-methyl group, perhaps impeding IgE binding.

R2 side-chain recognition by IgE; and the lack of appreciation of the extent of heterogeneity of the IgE response to cephalosporins.³ Despite published evidence of IgE antibody recognition of R2 side-chain structures, preoccupation with R1 group recognition prevails, often because of the failure to consider the possible involvement of more than 1 population of drug-reactive antibodies of different specificities in the same patient.^{2,3} In the present data, even a brief analysis of the observed reactions with different cephalosporins reveals obvious inconsistencies. For example, although 32 patients had positive skin test results to either cefotaxime or ceftriaxone or both, more than half of the patients had negative skin test results to cefepime and cefuroxime. These differences occur despite the presence of an identical R1 side chain in ceftriaxone, cefotaxime, and cefepime and a methoxyimino sequence in all the 4 drugs (Fig 1). Clearly, the common R1 structure is not the sole explanation for the allergic recognition in all 32 patients. For patient 79, recognition of the R2 ester group of cefuroxime and cefotaxime, perhaps *together* with the R1 methoxyimino, is the likely basis of the sensitivity (Fig 1). Skin test reaction patterns in patient 92 indicate that rather than recognition of the R1 side chain, it is the entire R1 side chain and the 2-ring structure with the attached R2 ester/ether linkage (with sterically unhindered O or S) that account for the patient's sensitivity (Fig 1). Presented data indicate other examples of R2 and/or whole molecule recognition. Close analyses of skin test reactivity patterns

supplemented with IgE antibody tests (especially inhibitions) superior in performance to the currently used cefaclor assay are likely to reveal further examples of cephalosporin allergies mediated by recognition of structures other than, or in addition to, the R1 side chains. In substituting cephalosporins to avoid allergy, similarities and differences between R1 groups need to be noted but failure to do likewise for R2 groups may lead to serious consequences for the occasional patient.

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