

EDITORIAL

Side-chain specific beta-lactam allergy

In the 1960s and 1970s numerous experimental studies were undertaken to define the participation of acyl side-chains in the formation of antigenic determinants of penicillins and cephalosporins. Dewdney in her excellent review of the immunology of antibiotics [1], concluded that these studies in general support an important role for side-chain specificities in the definition of overlapping anti-penicillin determinants. For cephalosporins even more drug-specific antibody has demonstrable side-chain specificity, in part because of greater lability of the cephalosporanate nucleus following aminolysis of the beta-lactam ring [2]. In fact, antibodies prepared in rabbits to cephalosporins with different *N*-acyl side-chains failed to crossreact at all, suggesting that virtually all drug-specific antibody was exclusively side-chain specific [2]. Thus, the existence of beta-lactam antibodies with distinct side-chain specificity has been appreciated for more than 25 years.

On the other hand the major antigenic determinant for penicillin immune responses is the penicilloyl specificity which appears to include the carbons of the beta-lactam ring and a portion of the adjacent carrier protein, with variable contributions from *N*-acyl side-chains [3-5]. The penicilloyl specificity is a neo-determinant in the sense that free penicillin molecules are 100-1000-fold less effective in inhibiting penicilloyl interactions than monovalent penicilloyl-amines or penicilloated proteins [6]. In contrast, the biological activity of side-chain specific beta-lactam antibodies is fully inhibitable by the parent beta-lactam drug, which in a therapeutic setting is present in substantial molar excess relative to the quantity of multivalent haptenated carriers. From these considerations one might speculate that side-chain specific drug antibodies are much less likely to be pathogenic than antibodies against neo-determinants like the penicilloyl group in which case the free drug provides little or no hapten inhibition. Since side-chain specific antibodies often predominate in immune responses to cephalosporins, one might also reasonably invoke the hapten inhibition theory as one plausible explanation for the apparently reduced allergenicity of cephalosporins compared with penicillins.

Early clinical studies were in good agreement that human IgE antibody responses to the major penicilloyl determinant could be readily ascertained using benzylpenicilloyl-protein or -polylysine for skin testing or *in-vitro* assays. Varying the side-chain in testing materials did not significantly improve the efficiency of diagnosis.

Solley *et al.* [7] reported in 1982 that the addition of ampicillin and methicillin skin tests to the usual benzylpenicillin-derived major and minor determinants increased the rate of positive skin tests among 778 prior penicillin reactors from 10.2 to 11.6%. If polylysine conjugates of ampicillin and methicillin were included in the skin test battery, the rate of positive results increased to 13.9%. None of the additional cases discovered using semi-synthetic penicillin skin tests were challenged or treated therapeutically, so the clinical risk associated with side-chain specific IgE was not determined. Warrington *et al.* [8] reported that the addition of semi-synthetic penicillins to a benzylpenicillin skin testing battery did not substantially increase the number of patients with positive skin tests among 253 Canadian adults and children with histories of penicillin allergy. Moss *et al.* [9] was able to elicit positive skin tests with semi-synthetic penicillins in some cystic fibrosis patients with negative benzylpenicillin skin test results, but high concentrations (≥ 20 mg/ml) of these drugs were required. Worldwide experience with penicillin skin testing is in general agreement that the use of benzylpenicillin reagents alone is sufficient to detect the vast majority of patients at risk for acute IgE-mediated penicillin reactions [8, 10-13]. The false negative reactions reported to date have commonly been mild and often self-limited. Thus, there has been ample reason to believe that side-chain specific beta-lactam reactions were either very rare or of little clinical consequence.

In 1988 Blanca *et al.* [14] in Malaga, Spain first challenged this comfortable view with a report of three cases of serious anaphylactic reactions to amoxycillin in patients whose standard benzylpenicillin skin tests were negative, and who had also had uneventful oral challenges with benzylpenicillin. Two of the three patients had positive skin tests to amoxycillin (20 mg/ml), and positive RAST tests with amoxycillin-polylysine conjugates. The third patient had hypotension, dyspnoea and generalized pruritus following a 5 mg oral amoxycillin challenge, despite negative skin and RAST tests with both benzylpenicillin and amoxycillin reagents. This seminal paper called into question the doctrine that side-chain specific antibodies are not likely to be the cause of serious acute allergic penicillin reactions.

In this issue of *Clinical and Experimental Allergy*, Blanca *et al.* [15] have made another significant contribution to this problem by providing systematic data on their experience in Spain with the use of both benzylpenicillin

and amoxycillin reagents both for IgE testing and provocation challenge. The results are both surprising and revealing. Among patients with histories of penicillin reactions referred for evaluation, 10 of 254 patients with negative skin tests and RASTs with benzylpenicillin major and minor determinants nevertheless went on to exhibit clinical reactions when subjected to an unmasked oral challenge with benzylpenicillin. This false negative rate of 3.9% is similar to the 4.1% rate reported by Solly *et al.* [7]. Half of these challenge reactions were delayed in onset, but the acute reactions included one case of hypotension and two cases of facial angioedema. More noteworthy is the fact that among 244 subjects with negative benzylpenicillin tests and oral challenges, eight cases exhibited a positive skin test and/or RAST to amoxycillin reagents, and another 13 had positive unblinded provocation tests with amoxycillin. While most reactions were mild and confined to skin eruptions, there was one case of hypotension and loss of consciousness following oral ingestion of 5 mg of amoxycillin.

One of the surprising findings of Blanca *et al.* [15] is that one-third of patients eventually diagnosed as allergic to penicillin by either immunological or provocation criteria were responsive *only* to amoxycillin reagents. This high rate of amoxycillin-restricted allergy could in part reflect that in Spain 45% of antibiotic prescriptions are for amoxycillin according to Blanca *et al.* [15]. This intensive use of amoxycillin in Spain may also account for the fact that 60% of the 288 Spanish patients with histories of penicillin reactions previously reacted to amoxycillin or ampicillin.

It has been well established that the di-amino penicillins such as ampicillin and amoxycillin produce non-urticarial rashes three to four times more frequently than other semi-synthetic penicillins, and induce rashes with very high frequency in patients suffering from diseases involving atypical or abnormal lymphocytes (mononucleosis, lymphocytic leukaemia, viral upper respiratory infections). Despite extensive study, the immunological basis for the relatively large numbers of reactions to ampicillin and amoxycillin remains obscure [16]. One common property of di-amino penicillins is their ability to form linear polymers of various lengths [17]. This has led to speculation that polymer formation either in the drug preparation itself, or subsequent to administration *in vivo* might allow presentation of a complete multivalent antigen more readily than for semi-synthetic penicillins which do not readily polymerize under physiological conditions [1]. Because in this sense amoxycillin is not a typical semi-synthetic penicillin, it is difficult to predict whether the results of Blanca *et al.* [15] with amoxycillin reagents will also apply to other semi-synthetic penicillins and cephalosporins.

Without confirmatory studies, it is also difficult to know whether local factors such as prescribing patterns and drug sources may have significantly influenced the Spanish experience with amoxycillin. Commercial lots of ampicillin have been shown to differ substantially in their degrees of intrinsic polymerization [18]. If the degree of polymerization is an important pathogenic factor, then the risk for drug-specific reactions could vary widely on a geographical basis based not only on prescription patterns but on the source or handling of drug product.

Blanca *et al.* have made a novel contribution to the controversy surrounding side-chain specific beta-lactam reactions by calling to our attention the fact that serious side-chain specific reactions can and do occur, and that at least for the case of amoxycillin (and perhaps ampicillin) additional testing with reagents of semi-synthetic origin may be usefully employed in appropriately selected patients. Additional studies will be needed to determine whether the Spanish experience can be generalized for other patient populations and further to define whether the experience with amoxycillin in Spain is likely to be applicable to other semi-synthetic penicillins in populations receiving them intensively, e.g. anti-pseudomonal penicillins in cystic fibrosis patients.

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