

Review article

Allergic reactions to penicillins. A changing world?

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Hypersensitivity reactions to betalactams are the most frequent type of adverse drug reaction mediated by an immunologic mechanism (25). Either immediate or delayed reactions can occur following administration of these therapeutic agents (15, 53, 70). In the last few years, several groups reported that immediate allergic reactions to betalactams can be selective for certain semisynthetic penicillins and this now appears to be fairly frequent among cases of penicillin allergy (3, 4, 8, 11, 60). In addition to these findings, several other new phenomena relating to allergic reactions to betalactam antibiotics have been observed. For example, a type of serum sickness induced by cefaclor has been reported (31, 42, 63, 71), and delayed reactions to aminopenicillins with good tolerance to benzylpenicillin (BP) have also been described (43, 55, 66, 74). Such observations suggest that new trends in antibiotic allergy may be appearing. Whether such trends are worldwide or whether there is variability from country to country is not yet known, though most probably any variation can be expected to reflect patterns of use (59).

In this review, trends relating to patterns of use and the incidence and type of allergic reactions to penicillins and related betalactams are analyzed. Furthermore, we proposed a common methodology in order to improve the diagnosis and management

of allergic patients, and ultimately our understanding of betalactam allergy.

Patterns of use of betalactams

Antibiotics account for 15-30% of world drug expenditure although availability varies widely from country to country, as well as from year to year (20). In 1982, the penicillins comprised the largest class within this group, and this predominance is still maintained. It was estimated that there was sufficient worldwide production capacity to provide every person with a therapeutic regimen each year. In 1983, the daily defined dose (ddd), a unit made for technical comparison, for amoxicillin (AX) was 10.34 in Spain, 4.9 in France, 4.7 in Australia, 3.04 in Canada, and 2.24 in the USA. The corresponding figures for the ddd of all other penicillins taken together were 1.1, 0.33, 0.2, 0.75, and 0.22, respectively (18). In all the countries studied, AX is the most widely used penicillin and exposure of the worldwide population to this drug is certainly higher than that to any other antibiotic (20, 32, 47). Trends in antibiotic use vary among countries, and between hospital and community practice. The analysis of drug use by office practice is a useful evaluation since it provides a good indication of the extent to which the population is exposed. In the USA, over

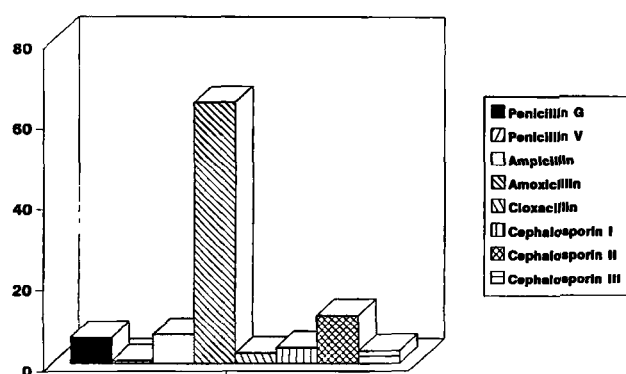


Fig. 1. Betalactams sold in Spain during 1993. Contribution in percentages of different derivatives.

a period of 4 years, important differences were observed in antibiotic prescription between hospital and outpatient practice (35, 47). Among the 25 most prescribed drugs in the USA in 1989, AX ranked number 9, followed by penicillin V (PV), which ranked 13, and ampicillin (AMP) 21 (7). Data on the volume of sales in Spain from 1982 to 1992 indicate a decrease in the use of BP by the parenteral route and a constant use of AX (31). In Spain, in 1993, AX comprised over 60% of total penicillin use (32). These data are presented in Fig. 1.

The analysis of betalactams used by office and family practice by North American doctors has been reported in several studies (22, 23, 35, 36, 47), and a graph summarizing these data over 10 years is presented in Fig. 2. It can be seen that, in addition to an increase in total betalactams prescribed, the increase in AX use was considerably greater than that for other betalactams.

Unfortunately, there are few studies available regarding adverse reactions to different betalactams and changes in the selectivity with time. In 1978,

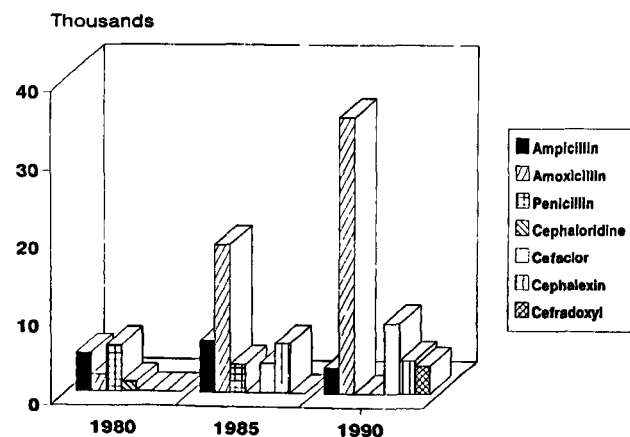


Fig. 2. Tendency in drug use in office practice by number of mentions in USA from 1980 to 1990.

Warrington et al. reported that in a large group of subjects allergic to betalactams the major and minor determinants of BP (BPO, MDM) were the most useful reagents for skin prick test diagnosis of penicillin allergy, and that the additional use of other reagents did not substantially increase the clinical diagnostic reliability (73). At the time of this early study, BP and AMP were the penicillins used most frequently. In a later study published by the same group in 1993, skin tests to minor determinants of AX and/or AMP accounted for 44% of skin test positivity alone. In this study, AX was involved in 33% of the subjects studied, BP in 30%, and AMP in 24% (60).

Immediate reactions to betalactams

The number of adverse reactions to betalactams reported in Spain since 1988 (8, 11, 15) reflects the relative use of different antibiotics by the population (9, 32). An analysis of the number of immediate reactions either selective for AX or nonselective to penicillins since we first reported AX allergy is presented in Fig. 3. It can be seen that there is a fairly constant ratio of selective reactions to AX/nonselective immediate reactions to other betalactams. No particular trend is observable. If data relating to consumption of penicillins are taken into account, it is clear that the consumption of AX has increased very considerably over the period of these studies (from 1986 onward). In recently published reports, the percentage of positive skin tests to minor determinants of AX or AMP in the total number of positive diagnoses of penicillin allergies was 26% (3), 22.5% (8), and 47.5% (60). Although these studies are not directly comparable, in all of them the contribution to skin test positivity of minor determinants of AX and/or AMP is very high and certainly

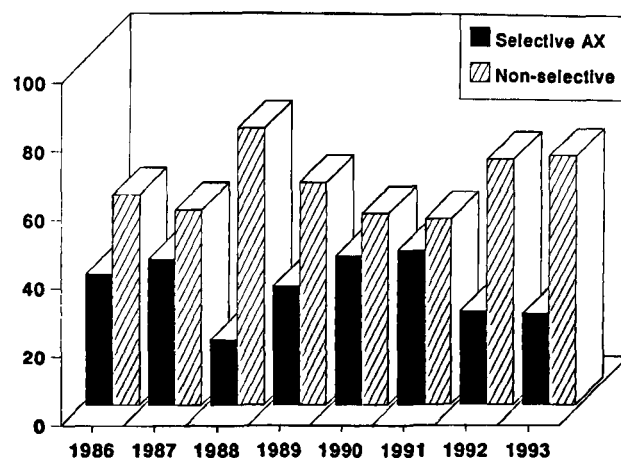


Fig. 3. Percentage of selective and nonselective reactions to penicillins from 1986 to 1993 in total of 280 positive cases.

different from previously reported data (73, 75). In all the above studies, the proportion of consumption of AX was over 60%, indicating that subjects taking AX in some instances develop a positive response to BPO and in others a selective response to AX (16). The lack of reports of specific side-chain reactions elsewhere seems puzzling since, as already stated, proportions of penicillin use similar to those in Spain are seen in other countries (20, 47, 60). This probably reflects a lack of appropriate and adequate skin test procedures, since in most countries subjects are diagnosed as allergic to penicillin by general practitioners (on the basis of clinical history) without other immunologic studies. In other instances, in spite of being evaluated by an allergy specialist, patients are not skin prick tested for minor determinants of AX, and *in vitro* IgE tests are not carried out. Although there may be genetic differences in the exposed populations, this is unlikely to account for the large differences in the reported incidence of selective allergy; for example, allergy to AX (61).

In a recent study a large group of subjects from a sexually transmitted diseases clinic was evaluated (27). All the positive cases were diagnosed with determinants from BP (BPO, MDM), and in this study no cases seemed to be selective only for aminopenicillins. The patients were selected before 1979, a period when the use of AX was still not predominant (22, 23).

The quantitation of *in vitro* IgE antibodies to penicillins has been a useful tool for us to study the IgE response to betalactams. The development of an *in vitro* sensitive method with a high density of hapten in the carrier has enabled our group to define the IgE specificities in cases with immediate reactions to penicillins (12–14). Furthermore, RAST inhibition studies enabled us to define the role of the different structures of penicillin with regard to the antibody binding site (12, 17) and to confirm that in AX the side-chain contributes in a relevant way to recognition by the antibody (46). Why subjects in some instances respond to different penicillin determinants and in others develop a selective response to AX is not known. Recent studies indicate that the pattern of response to AX is selectively restricted to this antibiotic (46) and that subjects allergic to AX re-sensitize to this drug but develop good tolerance after subsequent exposure to BP (paper in preparation). However, the possibility that this response is a result of the large use that is made of this drug is feasible, and a similar phenomenon has been reported with other drugs (64).

In a recent case cohort study carried out in 1991 in The Netherlands, AX was the second most important drug after glafenine in inducing an anaphylactic reaction (69).

Nonimmediate reactions to penicillins

Subjects often develop a nonimmediate response after taking a penicillin derivative. Various types of reactions that occur from several hours to 72 h or even 1 week after drug intake have been reported. Our group has used the term "nonimmediate reactions" to define these reactions, which in fact almost certainly represent a heterogeneous group in terms of symptoms and the immunologic mechanisms involved. Among the reactions that have been reported are contact dermatitis (45, 72), systemically induced contact dermatitis (57), rash and/or exanthema alone (2, 5, 33, 34, 51, 58, 62) or associated with viral infections (7, 21, 38, 48, 50), severe desquamative lesions (18), fever associated with exanthema (19, 55), urticaria (26, 56, 70), and toxic epidermal necrolysis (66).

Initially, Levine & Ovary reported the existence of positive skin tests to penicillin derivatives and suggested involvement of a cell-mediated immune response (40, 41). The appearance of rash associated with viral infections and other pathologic processes has also been reported (28, 52, 58). In many instances, the subjects tolerated the drugs after subsequent exposure (7). Nonimmediate reactions have been reported with AMP and AX (45, 51, 57, 70), BP (18, 39, 53), and cephalosporins (2, 54), and there may be more.

Although in exanthematic reactions an IgE mechanism may be involved and an immediate skin test response can be found (27), this is not common and in most instances a cell-mediated immune reaction or an unidentified idiosyncratic mechanism seems more likely. Skin biopsies with lymphomonocytic infiltrates have been reported (53, 55, 70, 74).

Patch tests have been considered a useful alternative for evaluating subjects with contact dermatitis (56, 72), but in recent studies the use of intradermal tests has proved a useful alternative for evaluating not only exanthematic but also urticaria reactions appearing from several hours to 48–72 h or even longer after drug intake (55, 67, 68).

Although more studies will be required to confirm these data, there would appear to be a trend toward an increase in the number of subjects with a delayed response to penicillins occurring nowadays related to the increased consumption of AX. In a recent study carried out by Romano et al. (55), 33/60 subjects with maculopapular rashes presented intradermal and patch test positivity to AMP and AX, and in three the response was also positive to BP. Eight of the 33 subjects developed desquamative lesions with associated fever. In a recent evaluation of 380 subjects with a history of cutaneous reactions to penicillins (68), 32 (8.4%) presented a nonimmediate reaction, developing symptoms 6 h or more after

drug exposure and in most cases after a period of 24–48 h or longer, and the percentage of intradermal skin test positivity was 68%. Interestingly, in 93% of these subjects, the response was selective for AX and/or AMP, and the tolerance to BP was established by administering the drug.

Reactions to cephalosporins

Among the betalactams, cephalosporins comprise the second most important group for treating different infectious diseases. They are used in hospitals more than the penicillins though they are also prescribed in office practice (22, 23, 36), particularly the first- and second-generation cephalosporins. As can be seen in Fig. 2, there is a trend toward increased consumption of cephalosporins. The great variability of the chemical structure of cephalosporins contributes to a heterogeneous specificity of the immunologic response. Quantitating IgE antibodies to cephalosporins is more difficult than to penicillins, although some assays have been reported (29). When allergic reactions to cephalosporins occur, it is due in some instances to cross-reactivity with penicillins, but in others the reaction is selective. Whether it is a side-chain-specific-reaction or a reaction to a new antigenic determinant or metabolite is not known because of the difficulty in identifying the structure of the epitope.

Cefaclor is a cephalosporin introduced in 1979 for treatment of Gram-positive infections. Initial evaluation of this drug indicated that it was effective and well tolerated and in only 2.3% of the cases did some kind of adverse reaction occur (37).

As shown in Fig. 2, an important increase in consumption took place between 1979 and 1990 (37). Soon after the drug was marketed, there were spontaneous reports in both Sweden and the USA that cefaclor was associated with a serum-sickness-like syndrome, and the risk seems to have been higher than with other drugs such as AX and sulfamethoxazole and also even other cephalosporins (31, 65, 71). Although serum sickness induced by cefaclor has been reported in many countries (31, 49, 50, 63) the greatest number of cases have been reported in the USA, the UK, Sweden, Canada, and Germany (44). A prospective study found that of 1017 children with 2513 courses of cefaclor and another 1009 with 2358 courses of AX, serum sickness occurred in five children who had taken cefaclor and in no children taking AX. The rate of serum sickness induced by cefaclor was established as two per 1000 prescriptions (44).

Serum sickness is a syndrome originally described by Von Pirquet in patients treated with antidiphtheric serum. Symptoms included fever, lymphadenopathy, arthralgias, cutaneous symptoms, and gas-

trointestinal disturbances with proteinuria. Various drugs have been involved (44). It has been considered a classical type III immune complex-mediated disease, but the serum sickness induced by cefaclor seems to represent a different pathophysiologic process, since circulating immune complexes have not been detected (30). An altered metabolism can generate toxic metabolites for lymphocytes (75), but these data need to be evaluated further and confirmed.

Conclusions and proposal for further work

In this review, we have been trying to link the recent advances made in the field of allergic reactions to betalactams (reviewed by Blanca et al. (15)) with the worldwide production, distribution, and use of these drugs. What initially seemed to be a provocative hypothesis (1) has been confirmed by observations made by different workers (3, 60). The changes seen over more than a decade in the market for betalactams has meant that patients are exposed to a far greater diversity of potentially haptenic and therefore potentially allergenic antibiotic chemical structures. Consequently, allergic reactions are now far less restricted than previously, when allergic reactions were mainly reported to penicillins and first-generation cephalosporins (6, 24, 40). Data concerning the use and prescription of penicillins in different countries will help us to understand the patterns of appearance of different reactions. Certainly, in those countries where a particular betalactam is used more commonly than benzylpenicillin, the use of major and minor determinants generated by these penicillins should be evaluated in order to determine whether this can be of diagnostic value (15). Often difficulties may arise with regard to approval for the use of antibiotics for skin testing, but it is the role of field investigators to determine the potential usefulness of such preparations. The measurement of specific IgE antibodies is another alternative that initially enabled our group to confirm the *in vivo* findings (10, 12). Although the sensitivity of the *in vitro* IgE assays is below that of skin tests (9, 70), it is in many instances a useful approach to defining the specificities (13, 45). In any event, details of methodological procedures are critical, and we have found important differences in sensitivity and specificity (14), particularly in assays for side-chain-specific IgE antibodies (17). Since the side-chain of betalactam antibiotics contributes importantly to IgE recognition, improvements in diagnostic testing that take this into account will enhance our understanding of the epidemiology, specificity, and cross-reactivity of penicillin allergy, and therefore lead to improvements in diagnosis and patient management.

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