

Delayed allergic reactions to betalactams

Four cases with intolerance to amoxicillin or ampicillin and good tolerance to penicillin G and V

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We present four cases of delayed allergic skin reactions to amoxicillin or ampicillin with good tolerance to benzyl penicillin and phenoxymethyl penicillin. The clinical symptoms reported by the patients, the intradermal skin tests and the controlled challenge results suggested that the mechanism was cellular mediated. In two patients these findings were supported by histopathological studies. Although delayed-type hypersensitivity reactions to betalactams with positive skin test seem rare, they can occur to penicillins in allergic patients. The production of these reactions by amoxicillin or ampicillin with good tolerance to benzyl penicillin and phenoxymethyl penicillin emphasizes the role of the side chain in inducing allergic reactions to betalactams.

Key words: amoxicillin; ampicillin; delayed hypersensitivity; side chain; specificity.

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The role of the acyl side chain in the specificity of immunological reactions to penicillins and/or cephalosporins has been established by several authors (1, 6, 8) although opinions differ (5, 11). These observations have important clinical implications since it has been reported that patients can tolerate some penicillins and develop an anaphylactic response after skin testing or taking other compounds of the same group where differences in the side chain are only slight (3, 4). Although most common allergic reactions to betalactams are Type I, IgE-mediated, other immunological mechanisms can also produce allergic reactions to these drugs (17). On the other hand, late or delayed immunological reactions with the specificity localised in the acyl side chain structure have also been reported (7, 13). In support of these findings we present evidence from clinical history, skin tests and controlled challenge that delayed type IV allergic reactions can be induced by either ampicillin (AMP) or amoxicillin (AX) and the patients can tolerate benzyl penicillin (PG) and phenoxymethyl penicillin (PV).

CASE REPORTS

Case 1

A 69-year-old woman developed a large local reaction in the area where an injection of 500 mg of AMP had been administered. Four years later, 24 h after an injection of AMP an exanthematic rash with pruritus appeared that persisted for 1 week. Immediate skin tests to benzyl penicilloyl (BPO) (5×10^{-5} M), minor determinant mixture (MDM) (2×10^{-2} M), AX (20 mg/ml), AMP (20 mg/ml) and cefamandole (CEF) (20 mg/ml) were negative. She reported having had a delayed local response at the sites of the skin tests that started after 12 h and persisted for several days. The patient was evaluated again when 12 h later she developed a skin infiltrate at the sites of the AX and AMP administrations. This maximized at 48 h (induration of 14×16 mm for AX and 18×15 mm for AMP) and subsided in 7 days. Skin tests

were negative to the other haptens used (BPO, MDM, CEF). Administration of 1 million units of BP by parenteral route was well tolerated, and after 1 week a capsule of PV (600,000 I.U.) three times a day for 3 days was also well tolerated. 5 mg of oral AMP induced a mild generalised pruritus, and exanthematic rash appeared 6 h after taking the drug and reached maximum response at 24–48 h. Skin biopsy determined after 48 h showed prominent mononuclear infiltration in the dermis with some neutrophils around the vessels. No signs of leucocytoclastic vasculitis were found.

Case 2

A 43-year-old man developed an exanthematic reaction to AX 4 months before assessment. After this episode he reported having had good response to PG parenterally. Immediate skin tests to BPO, MDM, AX, AMP and CEF as used above were negative. He noticed a local swelling after 24 h at some of the skin test sites. A repetition showed a negative immediate response to all the haptens and after 24 h a local induration appeared at the AX and AMP sites (18×16 mm and 16×17 mm) but was negative at the others. The response maximized at 72 h and declined in 10 days, (results are presented in Fig. 1 A). A biopsy taken at the site of induration showed mononuclear cell infiltration with edema of the vessels and fibrin deposition but no evidence of leucocytoclastic vasculitis. The patient tolerated 1 million units of PG parenterally and after an interval of 1 week a capsule of PV (6×10^5 I.U.) was given every 8 h with good tolerance. An initial dose of 5 mg AX was given and as no response developed 500 mg were administered. A mild exanthematic rash appeared on the trunk and lower extremities requiring treatment with antihistamines and corticoids.

Case 3

A 40-year-old woman developed an urticaria 20 years ago after receiving an unknown antibiotic

parenterally. Seven years later an unknown antibiotic, taken orally, induced a similar reaction 8 h after the first capsule. Four months before evaluation a fixed drug eruption appeared after taking trimetropin sulphametoxazol. After skin testing with the five derivatives mentioned above a positive response appeared to AX (18×20 mm) and AMP (16×16 mm), the others being negative. Administration of PG and PV following the procedure described was well tolerated. After receiving 5 mg AX orally an exanthematic rash appeared on the patient's arms and neck.

Case 4

A 23-year-old woman with systemic sclerosis developed an exanthematic reaction 7 years ago after taking 500 mg AX every 8 h for 2 days. Three months later after taking a capsule of AX (500 mg) a reaction appeared after 6 h that was more intense than the previous one. Later she reported having had pruritus after a local anesthetic but no skin lesion or other complaint. Immediate skin test to PBO, MDM, AX, AMP and CEF were negative. She reported having had a late response that started after 24 h and persisted for several days. Skin tests were repeated. Immediate response to the five compounds was negative. After 24 h a positive local reaction appeared at the site of AX and AMP that maximized at 24–48 h (18×17 mm for AX and 16×18 mm for AMP) and decreased slowly in 1 week leaving a small desquamative lesion. Results can be seen in Fig. 1b. The patient skin biopsy. The administration of PG parenterally and PV orally was well tolerated. A challenge with AX and AMP was not made due to an underlying disease although at the moment of the study she was asymptomatic.

DISCUSSION

Although non-immediate allergic reactions to penicillins have not been evaluated as thoroughly as type I, IgE mediated (11, 16), several immunological mechanisms have been

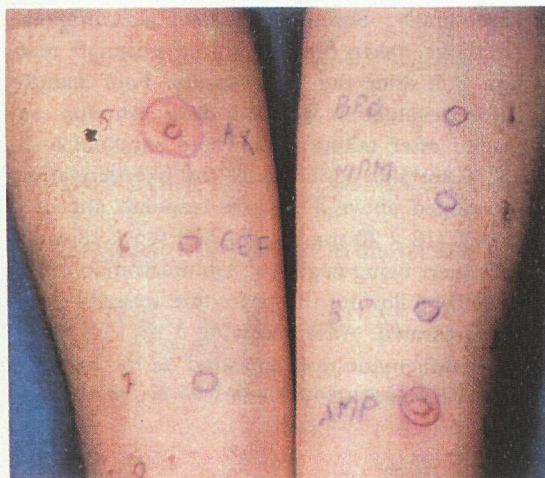


Fig. 1 A (right). Intradermal skin tests to benzyl penicilloyl (BPO), 10^4 (minor determinant mixture), ampicillin (AP), amoxicillin (AM), cefamandole (CF), saline diluent (-) and histamine (+). The small circles show the area of the papula after the intradermal injection. The large circle represents the wheal area produced by histamine after 20 min. No immediate reaction occurred with any of the haptens used. In the sites where AP and AM were injected a local inflammatory response appeared that maximized at 48 h (patient 2).

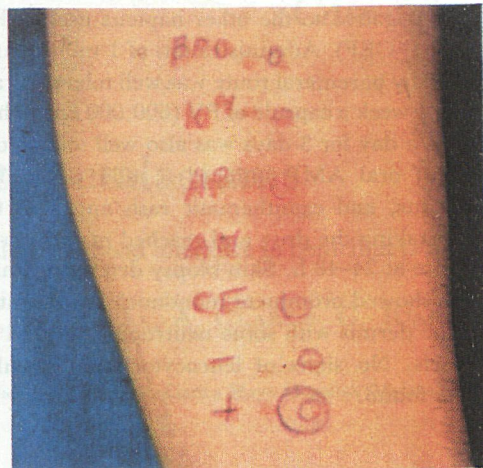


Fig. 1 B (left). Intradermal skin test to BPO, MDM, BP (benzyl penicillin), AMP (ampicillin), AX (amoxicillin) and CEF (cefamandole). In the sites of AMP and AX, the larger circles show the inflammatory response areas after 48 h. Immediate skin tests to all haptens used were negative (patient 4).

involved in their induction (14, 16). An Arthus-like phenomenon has been proposed by some authors, although this has not been sufficiently proved (14). A late reaction can be part of an immediate IgE-mediated one (12). Also, a late cutaneous reaction in the absence of an immediate response has been reported, although the immunological mechanism has not been established (7). Considering the clinical characteristics, skin test results and pathological studies of our cases, those mechanisms can be discarded. Another possibility is the delayed type, mediated by sensitized T lymphocytes (7, 9). The interval between the appearance of the skin reaction and cellular infiltration in two of our patients suggests that this could be the mechanism involved. Although skin rashes to AMP and AX can be produced by a non-immunological phenomenon, in some instances, related to a concomitant disease (6, 16), in our cases the appearance of symptoms after challenge when the patients were asymptomatic suggests an immunological mechanism

and no interference from a concomitant disease. Such reactions have also been reported by others (9, 16).

The occurrence of positive delayed skin tests in allergic reactions to penicillins has not been sufficiently evaluated (1, 16). However, they appear to be infrequent (10). Moreover, data about the sensitivity and specificity of delayed skin tests in groups of patients allergic to betalactams are lacking (1, 16). In our cases the association of clinical symptoms with delayed positive skin test and challenge to AMP and AX, with negative skin test to BPO and MDM, and good tolerance after challenge to PV and PG, suggest an immunological mechanism mediated by sensitized T cells that recognise the determinant in the side chain. In our cases the chemical structure of the penicillin derivative appears crucial. The role of the acyl side chain has also been reported by others. Stejkal et al. (13) have found workers exposed to bacampicillin who developed positive *in vitro* lymphocyte response and patch test positivity with good

response to PG. Vorhorst et al. have also reported a delayed type response to ampicillin in a patient with an exanthematic rash with good tolerance in patch testing to benzyl penicillin (15). In this work we give evidence to support the existence of delayed response to AMP or AX with good tolerance to PG and PV, thus emphasizing the role of the acyl side chain in inducing specific cellular-mediated immunological reactions. The frequency of this phenomenon in a population with allergic reactions to penicillins is unknown to us, although it is being evaluated.

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