

Allergic reactions to ampicillin. Studies on the specificity and selectivity in subjects with immediate reactions

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Summary

Background Ampicillin (AMP) is a drug that has been prescribed extensively. Reactions that have been reported include exanthema, desquamative contact eczema, urticaria and anaphylaxis. Experimental evidence indicates that the side chain of AMP is a structure that may induce a selective immune response either at the humoral or lymphocyte T-cell level. With regard to IgE reactions, the selectivity and specificity of the response needs to be studied in humans.

Objectives To study the specificity of the IgE response in a group of subjects who had an immediate allergic reaction after the administration of AMP.

Methods Subjects developing an immediate response (anaphylaxis or urticaria) after the administration of AMP or an aminopenicillin derivative with the same side chain as AMP were studied. Skin tests were made to determinants generated from benzyl penicillin (BP): benzyl penicilloyl (BPO) and minor determinant mixture (MDM), as well as amoxicillin (AX) and AMP. Specific IgE antibodies were determined to benzyl penicilloyl polylysine (BPO-PLL), amoxicilloyl-polylysine (AX-PLL) and ampicilloyl-polylysine (AMP-PLL). The specificity of the IgE antibody response was studied by RAST and RAST inhibition. Subjects were classified in three categories: group A: those who were skin test and/or RAST positive to determinants derived from benzylpenicillin, group B: those who were negative to determinants derived from benzylpenicillin but were skin test and/or RAST positive to determinants derived from AX and AMP and group C: those who were exclusively positive to determinants derived from AMP.

Results A total of 48 subjects was included in the study. In group A there were 35 cases, in group B 10 cases, and in group C three cases. RAST inhibition studies showed that in some instances the side chain of AMP could induce specific responses with a variable degree of crossreactivity between BP and AX.

Conclusions Although AMP can induce an immediate IgE response in subjects allergic to betalactams and the structure of the side chain may contribute to the specificity of the response, our results indicate that in most instances crossreactivity with the other penicillins exists and that in the groups studied selective reactions to just AMP derived determinants were uncommon.

Keywords: ampicillin, IgE-mediated reactions, crossreactivity, benzyl penicillin, amoxicillin

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Introduction

Although IgE antibodies to penicillin derivatives recognize

References

- 1 Amos HE. Antigenic determinants of the penicillin molecule. In: Amos HE, ed. *Allergic drug reactions*. Oxford: Edward Arnold, 1976:64–72.
- 2 Dewdney JM. Immunology of the antibiotics. In Sela M, ed. *Antigens 5*, New York:Academic Press, 1977; 73–245.
- 3 Blanca M, Vega JM, Garcia J et al. New aspects of allergic reactions to betalactams. Cross-reactions and unique specificities. *Clin Exp Allergy* 1994; 24:407–15.
- 4 Nishida K, Kinoshita Y, Atsumi T, Shibata K, Horiuchi Y. The analysis of combining sites of rabbit antipenicilloyl antibodies. *Immunochemistry* 1972; 9:1195–202.
- 5 Bondaruk J, Curcio-Vonlanthen V, Schneider CH. Basic aspects related to penicillin-allergy skin testing: on the variability of the hapten–paratope interaction. *Allergy* 1995; 50:671–6.
- 6 Stejskal VDM, Forsbeck M, Olin R. Side chain specific lymphocyte responses in workers with occupational allergy induced by penicillins. *Int Arch Allergy Appl Immunol* 1987; 82:461–4.
- 7 Nagakura N, Souma S, Shimizu T, Yanaghiara Y. Anti-ampicillin monoclonal antibodies and their cross-reactivities to various β -lactams. *J Anti Chemothe* 1991; 28:357–68.
- 8 Blanca M. The contribution of the side chain of penicillins in the induction of allergic reactions. *J Allergy Clin Immunol* 1994; 94:562–3.
- 9 Solley GO, Gleich GJ, Van Dellen RG. Penicillin allergy: clinical experience with a battery of skin tests reagents. *J Allergy Clin Immunol* 1982; 69:238–44.
- 10 Silviu-Dan F, McPhillips S, Warrington RJ. The frequency of skin test reactions to side-chain penicillin determinants. *J Allergy Clin Immunol* 1993; 91:694–701.
- 11 Miranda A, Blanca M, Vega JM et al. Cross-reactivity between a penicillin and a cephalosporin with the same side chain. *J Allergy Clin Immunol* 1996; 98:671–7.
- 12 Blanca M, Mayorga C, Perez E, Suau R. Determination of IgE antibodies to the benzyl penicilloyl determinant. A comparison between poly-L-lysine and human serum albumin as carriers. *J Immunol Methods* 1992; 153:99–105.
- 13 Mzingo R, Folkers K. *The Chemistry of Penicillins*. New York, Princeton University Press, 1949:634–8.
- 14 Hobby GL. New Penicillins produced, in *Penicillin*. Meeting the challenge. Yale University Press, New Haven 1985:213.
- 15 Bierman CW. Reactions associated with ampicillin therapy. *JAMA* 1972; 220:1098–70.
- 16 Shapiro M, Townsend TR, Rosner B, Kass EH. Use of antimicrobial drugs in general hospitals. II. Analysis of patterns of use. *J Infect Dis* 1979; 139:698.
- 17 Blanca M. Allergic reactions to penicillins. A changing world? *Allergy* 1995; 50:777–82.
- 18 Levine BB. Skin rashes with penicillin therapy. *NEJM* 1972; 286:505–7.
- 19 Redmond AP, Levine BB. Delayed hypersensitivity to penicillin in man. *J Allergy* 1967; 39:51–6.
- 20 Fellner MJ, Ball EH, Allyn B, Baer RL. Delayed hypersensitivity to penicillin: clinical significance and hyposensitization after therapy *JAMA* 1969; 210:2061–2.
- 21 Romano A, Di Fonso M, Papa G, Venuti A. Evaluation of adverse cutaneous reactions to aminopenicillins with emphasis on those manifested by maculopular rashes. *Allergy* 1995; 50:113–8.
- 22 Prieto C, Gamboa PM, Zugazaga M, Fernandez JC. *Allergol et Immunopathol* 1990; 18:141–8.
- 23 Gonzalez J, Guerra F, Moreno C, et al. Assessment of a self-defined protocol on patients with adverse reactions to β -lactam antibiotics. *Allergolo et Immunopathol* 1992; 20:184–9.
- 24 Dewdney JM, Wheeler AW. The formation of antigenic polymers in aqueous solutions of betalactams antibiotics. *Immunology* 1971; 21:517.
- 25 Batchelor FR, Dewdney J, Janet M, Feinberg GJ. A penicilloilated protein impurity as a source of allergy to benzyl penicillin and 6-amino penicillanic acid. *Lancet*; i:1175–8.
- 26 Larsen C, Bundgaard H. Polymerization of penicillins. V. Separation, identification and quantitative determination of antigenic polymerization products in ampicillin sodium preparations by high performance liquid chromatography. *J Chroma* 1978; 147:143–50.
- 27 Blanca M, Vega JM, Garcia J et al. Allergy to penicillin with good tolerance to other penicillins; study of the incidence in subjects allergic to beta-lactam. *Clin Exp Allergy* 1990; 20:475–81.
- 28 Audicana M, Bernaola G, Urrutia I et al. Allergic reactions to betalactams: studies in a group of patients allergic to penicillin and evaluation of cross-reactivity with cephalosporin. *Allergy* 1994; 49:108–13.
- 29 Daxun Z, Adriansson J, Martin A. Diagnostic capabilities of penicillin-based structures as tools in the in vitro diagnosis of penicillin allergy. *J Invest Clin Immunol* 1992; 2:240–6.