

Selective allergic reactions to clavulanic acid

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Clavulanic acid (CL) is a β -lactam antibiotic with weak antibacterial activity, but it is a potent inhibitor of β -lactamases. In association with amoxycillin (AX) it has great antimicrobial activity and is increasingly prescribed in daily medical practice.

We present two cases of selective adverse reactions to CL with good tolerance to other β -lactam antibiotics in which a type I immunologic mechanism is probably implicated. To the best of our knowledge, these are the first reported cases of selective allergy to CL.

CASE REPORTS

Case 1

Four months before consultation, a 16-year-old boy received amoxycillin-clavulanic acid (AX/CL) (500/125 mg). Forty minutes after the intake of the first capsule, he was first seen with dyspnea and generalized urticaria. The reaction subsided in the next hour after the administration of methylprednisolone and dexchlorpheniramine. He had previously received AX/CL with good tolerance. Since the described reaction he has not taken β -lactam antibiotics.

He also had grass pollen-induced rhinoconjunctivitis. His father had hand contact dermatitis in response to chromium salts. The patient's total IgE was 460 IU/ml (CAP system; Pharmacia, Uppsala, Sweden). Forced basal spirometry was normal.

Case 2

Three months before consultation, a 15-year-old girl received AX/CL (500/125 mg). One hour after the first dose she experienced a mild generalized urticaria, which subsided spontaneously in the next 2 hours. AX/CL

Abbreviations used

AX: Amoxycillin

CL: Clavulanic acid

HRT: Histamine release test

administration was stopped. Two months later, she again received AX/CL (500/125 mg), and 10 minutes after she took the first capsule she had generalized urticaria, facial edema, hypotension (blood pressure reported as "undetectable" when she arrived at the emergency room), and loss of consciousness. She received epinephrine, dexchlorpheniramine, and methylprednisolone with rapid recovery.

There was no personal or family history of atopy. Skin test responses to a battery of common inhalants were negative. Total IgE was 250 IU/ml (CAP system, Pharmacia).

RESULTS

Prick and intradermal tests were performed with benzylpenicilloyl poly-L-lysine, minor determinant mixture (Allergopen; Allergopharma, Hamburg, Germany), and benzylpenicillin 10,000 IU/ml; AX, ampicillin, and cloxacillin at 20 mg/ml; cefazolin, cefamandole, cefotaxime, ceftazidime, aztreonam, and imipenem at 2.5 and 25 mg/ml. The results of all these skin tests were negative in both patients.

Results of skin tests with CL 1 mg/ml and 10 mg/ml (Beecham, Toledo, Spain) in a saline solution were positive in both patients. No late reactions were observed (Table I). Results of these skin tests were negative in 20 control subjects who tolerated CL.

A histamine release test (HRT) was performed according to an automated fluorimetric method¹ with benzylpenicillin 1.6, 8, 40, and 200 IU; AX 3.2, 16, 80, and 400 μ g; and CL 1.6, 8, 40 and 200 μ g. A release greater than 10% over basal value was considered positive. In patient 1, the HRT result was negative with benzylpenicillin and AX. A dose-related positive HRT result was obtained with CL (18%, 25%, 31%, 25%), with a maximum release at 40 μ g, then a decrease at 200 μ g. The

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TABLE 1. Results of in vivo and in vitro tests with clavulanic acid

Test	Patient 1	Patient 2
CL 1 (mg/ml)		
SPT	4 × 3 mm	Negative
ID	25 × 14 mm (PS)	11 × 9 mm
CL 10 (mg/ml)		
SPT	6 × 5 mm	Negative
ID	ND	17 × 11 mm (PS)
Histamine release (maximum release)	31%	Not conclusive
RAST	Negative	Negative
Oral challenge (eliciting dose)	Positive (15 mg)	ND

Control group: 20 subjects did not react to skin tests and five subjects did not react to HRT for the concentrations tested. SPT, Skin prick test; ID, intradermal skin test; PS, pseudopods; ND, not done.

result of the HRT was not conclusive in patient 2, because her basophils did not liberate histamine when triggered with anti-IgE. Results of this assay were negative for five control subjects.

RAST responses to benzylpenicilloyl and fenoxymethylpenicilloyl, AX, and ampicillin (CAP System, Pharmacia) were negative for both patients.

Human serum albumin-conjugated CL² was coupled to cyanogen bromide-activated filter paper disks. CL disks were incubated (in duplicate) for 24 hours with the patients' sera. Afterward, a standard RAST technique was carried out (Phadebas RAST, Pharmacia). Serum samples from 10 atopic subjects were used as controls. RAST responses to CL failed to demonstrate specific IgE in both patients and control subjects.

The patients were challenged by means of a single-blind, placebo-controlled protocol with benzylpenicillin, fenoxymethylpenicillin, AX, ampicillin, cloxacillin, and CL as β -lactam drugs and ditazol and pemoline as oxazolic compounds. Only one drug or placebo was given on any one day. Progressively increasing doses were administered until the therapeutic dose was reached. The challenges were performed with careful monitoring of the patients, and full emergency therapy was provided. Written informed consent was given by the patients' parents.

Both patients tolerated therapeutic doses of benzylpenicillin, fenoxymethylpenicillin, AX, ampicillin, cloxacillin, ditazol, and pemoline. Patient 1 had generalized urticaria, conjunctivitis, dyspnea, and a 27% fall in basal forced expiratory volume in 1 second, 45 minutes after the ingestion of 15 mg of CL. The reaction subsided when symptoms were treated. Patient 2 was not challenged with CL because of the severity of the previous reaction and the presence of positive skin test results.

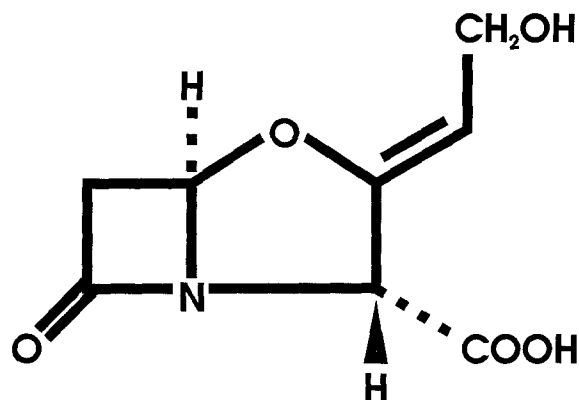
DISCUSSION

We present two cases of immediate adverse reactions to the combination of AX and CL in which a selective reactivity to CL is demonstrated. Results of skin tests to benzylpenicilloyl poly-L-lysine, minor determinant mixture, benzylpenicillin, and AX, as well as RAST responses to penicilloyl G and V and AX were negative. Both patients tolerated benzylpenicillin, fenoxymethylpenicillin, AX, and other β -lactams. However, skin test responses to CL were positive in both patients (negative in 20 control subjects), and a positive HRT response to CL was obtained in patient 1 (negative in five control subjects). The selectivity of the reaction was confirmed in patient 1 by means of an oral challenge with CL. Although we failed to demonstrate serum-specific IgE to CL, the studies performed suggest that a type I immunologic mechanism was implicated in these adverse responses.

CL is a β -lactam drug derived from 6-aminopenicillanic acid, which lacks the side chain in the C6 position. The secondary ring is an oxazolidine one instead of the thiazolidine ring of penicillins (Fig. 1).

When the β -lactam carbonyl group of penicillins reacts with protein amino groups, this leads to the formation of benzylpenicilloyl. Three possible determinants have been identified on benzylpenicilloyl: the side chain, the thiazolidine ring, and the new antigenic determinant.³ Although CL may share the new antigenic determinant with penicillins, we did not detect specific IgE to penicilloyl in our patients.

To determine the involvement of the oxazolidine ring of CL in the patients' reactions, we studied their tolerance to drugs containing this structure: cloxacillin, pemoline, and ditazol. Skin



CLAVULANIC ACID

FIG. 1. Chemical structure of CL.

test responses to cloxacillin were negative, and both patients tolerated these three drugs.

Our two patients react exclusively to CL but tolerate related drugs. This may be due to the differences in CL structure, which can greatly influence the specificity of the immunologic response. On the other hand, CL metabolism is strikingly different from that of penicillin and gives rise to various products which are not chemically related to those derived from benzylpenicillin.⁴ We do not know which hapten/s of CL induce our patients' reactions, but they do not seem to be cross-reactive with the determinants of benzylpenicillin.

Edwards et al.⁵ found that CL had very low immunogenic and allergenic potential, which was attributed to its complex immunochemistry: the reaction of CL with protein amino groups produces a heterogeneous conjugate with different small haptenic groups possessing low epitope densities. However, we have found that CL can induce severe adverse reactions by a probable type I immunologic mechanism. Further studies are needed to establish the allergenicity of CL.

REFERENCES

1. Siraganian RP. Histamine release and assay methods for the study of human allergy. In: Rose NR, Friedman H, eds. *Manual of clinical immunology*. Washington: American Society for Microbiology, 1976:603-15.
2. Levine BB, Ovary Z. Studies on the mechanism of formation of the penicillin antigen. III. The N-(D- α -benzylpenicilloyl) group as an antigenic determinant responsible for hypersensitivity to penicillin G. *J Exp Med* 1961;114:875-904.
3. De Haan P, de Jonge AJR, Verbrugge T, Boorsma DM. Three epitope-specific monoclonal antibodies against the hapten penicillin. *Int Arch Allergy Appl Immunol* 1985;76:42-6.
4. Haginaka J, Yasuda H, Uno T, Nakagawa T. Degradation of clavulanic acid in aqueous alkaline solution: isolation and structural investigation of degradation products. *Chem Pharm Bull (Tokyo)* 1985;33:218-44.
5. Edwards RG, Dewdney JM, Dobrzanski RJ, Lee D. Immunogenicity and allergenicity studies on two betalactam structures, a clavam, clavulanic acid, and a carbapenem: structure-activity relationships. *Int Arch Allergy Appl Immunol* 1988;85:184-9.