

Letter to the Editor

Selective allergic reactions to clavulanic acid: A report of 9 cases

To the Editor:

Clavulanic acid is a β -lactam antibiotic with weak antibacterial activity but is a potent inhibitor of β -lactamases. In clinical practice clavulanic acid is available as a combination product with amoxicillin.¹

Skin prick and intradermal tests are the main diagnostic methods used to confirm clinical hypersensitivity after immediate allergic reactions to β -lactam antibiotics.² Prior studies have demonstrated that quantification of *in vitro* basophil activation carried out by means of flow cytometry can be reliable for measuring IgE-dependent, allergen-specific responses in patients who are allergic to β -lactams,³ as well as to clavulanic acid.²

We describe 9 cases of allergic reactions to clavulanic acid that were diagnosed in our department between 2004 and 2009. We used skin test results and performed basophil activation tests to detect the presence of specific IgE.

Nine patients, 4 women and 5 men, who were 19 to 58 years of age (mean age, 42.4 years) were referred to our allergy department with adverse reactions to amoxicillin–clavulanic acid. Clinical symptoms appeared immediately (within 60 minutes of intake) in 5 of the patients and after 2 hours in the other 4 patients. The symptoms reported were maculopapular rash in 3 patients, urticaria in 3 patients, urticaria accompanied by angioedema in 2 patients, and anaphylaxis (generalized erythema with pruritus, hives, and dyspnea) in 1 patient. In 3 patients the reaction also involved other drugs. In 2 patients paracetamol and amoxicillin–clavulanic acid were involved, and in the third patient paracetamol, acetylcysteine, and amoxicillin–clavulanic acid were the implicated drugs. We performed skin tests and single-blind oral challenges with the other implicated drugs with negative results, and therefore these drugs were ruled out as casual. None of these subjects reported prior adverse drug reactions. All patients had previously received amoxicillin–clavulanic acid without adverse events. The characteristics of the reactions and patients' ages are shown in Table I. The patients consented in writing before skin tests, and controlled challenge tests were performed, although institutional review board approval was not obtained.

Results of skin prick and intradermal tests with benzylpenicilloyl poly-L-lysine as the major determinant at a concentration of 0.04 mg/mL and a minor determinant mixture (benzylpenicillin sodium, benzylpenicilloic acid, and sodium benzylpenicilloate) at 0.5 mg/mL were negative in all patients (Diater SA, Madrid, Spain). In addition, results of skin prick and intradermal tests with benzylpenicillin (10,000 IU/mL; Normon SA, Madrid, Spain), amoxicillin (20 and 25 mg/mL; GlaxoSmithKline SA, Madrid, Spain), ampicillin (20 mg/mL, Normon SA), cefuroxime (2 mg/mL, GlaxoSmithKline SA), and ceftazidime (2 mg/mL; Combino Pharm SL, Barcelona, Spain) were all negative. Results of skin prick tests with amoxicillin–clavulanic acid (20 mg/mL, GlaxoSmithKline SA) were also negative in the 9 patients. Results of intradermal tests with amoxicillin–clavulanic acid at 20 mg/mL were positive in all patients except for patient 2. Skin tests with amoxicillin–clavulanic acid were performed

TABLE I. Characteristics of the reactions

Patient no.	Age (y)	Year of reaction	Latency	Symptoms
1	19	2004	2 d	Maculopapular rash
2	50	2004	4 d	Urticaria
3	52	2008	45 min	Maculopapular rash
4	33	2008	2 h	Urticaria and angioedema
5	43	2008	45 min	Anaphylaxis
6	40	2008	45 min	Urticaria and angioedema
7	58	2008	30 min	Maculopapular rash
8	41	2009	30 min	Urticaria
9	46	2009	4 h	Urticaria

with the intravenous suspension of this drug. Control subjects were subjects with a history of an adverse reaction to β -lactams that was not confirmed (negative skin test and oral challenge results). Specific IgE antibodies against penicillin V, penicillin G, amoxicillin, and ampicillin (CAP-FEIA; Phadia, Uppsala, Sweden) were less than 0.35 UI/mL in all patients.

Because skin test results and specific IgE levels for amoxicillin were negative and skin test results to amoxicillin–clavulanic acid were positive in 8 of 9 patients, single-blind oral challenges were performed with amoxicillin. In addition, patient 2, who had a negative skin test result with amoxicillin–clavulanic acid, underwent a single-blind oral challenge with amoxicillin–clavulanic acid because this was the drug suspected in the original reaction referred by the patient. Oral challenges were performed with amoxicillin (125, 250, and 500 mg) and amoxicillin–clavulanic acid (125/31.25, 250/62.5, and 500/125 mg), increasing doses at 1-hour intervals. In nonimmediate reactions (patients 1, 2, 4, and 9) the therapeutic dose was subsequently taken at home every 8 hours for 7 days. The result of a single-blind oral challenge with amoxicillin–clavulanic acid in patient 2 was positive, with a delayed reaction. Twenty-four hours after the oral challenge with amoxicillin–clavulanic acid, (cumulative dose of 1,875/468.75 mg), the patient experienced a generalized maculopapular rash that resolved over 48 hours with antihistamines and corticosteroids. Results of single-blind oral challenges with amoxicillin in all patients, including patient 2, were negative.

In 2009, we obtained for the first time purified clavulanic acid (Normon SA) for patient testing. Clavulanic acid is inherently unstable in solution, requiring the use of excipients, either Avicel (cellulose) or Syloid (silica). Commercially, Avicel (Normon SA) is used in oral tablets, and Syloid (Normon SA) is used for oral suspensions. For skin testing, clavulanic acid was mixed one to one with one of the excipients, and concentrations of 10 mg/mL (both of clavulanic acid and excipient) were used for skin prick testing, with concentrations of 0.1 and 1 mg/mL used for intradermal testing. We contacted all of the patients previously given diagnoses of suspected clavulanic acid sensitivity, and all agreed to testing. All subjects had negative skin prick test responses at 10 mg/mL clavulanic acid and excipient and negative intradermal test results with 0.1 mg/mL. However, 7 of 9 patients had positive intradermal test results with 1 mg/mL clavulanic acid (patients 1 and 2 had negative results). Skin prick and intradermal test results with clavulanic acid and excipients were negative in 10

TABLE II. Results of the allergy study

Case	Skin tests	Specific IgE	Oral challenge	Clavulanic acid skin tests	Basophil activation test
1	IDR AM-CL + IDR AM –	<0.35 kU/L	AM –	Negative	Basal stimulation
2	IDR AM-CL – IDR AM –	<0.35 kU/L	AM CL + AM –	Negative	CL+Syloid +
3	IDR AM-CL + IDR AM –	<0.35 kU/L	AM –	Positive	Basal stimulation
4	IDR AM-CL + IDR AM –	<0.35 kU/L	AM –	Positive	CL+Syloid +
5	IDR AM-CL + IDR AM –	<0.35 kU/L	AM –	Positive	CL+Avicel +
6	IDR AM-CL + IDR AM –	<0.35 kU/L	AM –	Positive	Basal stimulation
7	IDR AM-CL + IDR AM –	<0.35 kU/L	AM –	Positive	CL+Syloid +
8	IDR AM-CL + IDR AM –	<0.35 kU/L	AM –	Positive	Not assessable
9	IDR AM-CL + IDR AM –	<0.35 kU/L	AM –	Positive	Negative

AM, Amoxicillin; AM-CL, amoxicillin-clavulanic acid; CL+Syloid, clavulanic acid and Syloid; CL+Avicel, clavulanic acid and Avicel; IDR, intradermal test.

control subjects. These subjects were selected from our practice based on a history of a prior adverse event when treated with amoxicillin–clavulanic acid but who had subsequently tolerated a challenge with amoxicillin–clavulanic acid.

As previously described,³ flow cytometric analysis of CD63 expression by basophils was performed after *in vitro* allergen-specific stimulation with clavulanic acid (with Syloid and with Avicel) at concentrations of both 0.05 and 0.5 mg/mL. Excipient and clavulanic acid concentrations were the same as used for skin testing. Five subjects with prior negative challenge results to amoxicillin–clavulanic acid served as negative control subjects. The basophil activation test results were positive in 4 patients at both concentrations, 3 with clavulanic acid with Avicel and 1 with clavulanic acid with Syloid. Three patients had a basal stimulation of basophils, probably because of nonspecific stimulation; therefore the results were not assessable. One patient had negative results, and another was not assessable because of a low number of basophils. All control subjects had negative results in specific basophil activation with both concentrations of clavulanic acid and both excipients. The results of allergy study are shown in Table II.

Allergic reactions to β -lactam antibiotics are the most frequent cause of adverse drug reactions caused by IgE-mediated mechanisms.⁴ Clavulanic acid has been associated with very few allergic reactions, suggesting a low allergenic potential.⁵

The diagnosis of clavulanic acid hypersensitivity is complicated by limited availability of clavulanic acid in a stable solution for skin or *in vitro* testing.⁵ We obtained clavulanic acid alone and performed skin prick and intradermal tests with positive results in 7 of 9 patients with suspected allergy to clavulanic acid and in none of 10 subjects who tolerated amoxicillin–clavulanic acid. Negative skin test results with amoxicillin–clavulanic acid in 2 patients might be explained by a 5-year time period between the original adverse reaction and skin tests with amoxicillin–clavulanic acid and the purified clavulanic acid. Skin test reactivity to penicillin decreases annually after an allergic reaction to the antibiotic. Therefore 73% continued to have a positive response within 1 year of the reaction, 57% between 1 and 10 years, and

22% at 10 years or more after the reaction.⁶ Therefore 2 of 9 patients might have lost skin test reactivity after the passage of 5 years. This point is speculative.

Despite the extensive use of amoxicillin–clavulanic acid, few reports of a drug allergy to clavulanic acid have been reported.^{1,2,5,7-12} In the first article Fernández-Rivas et al¹ described 2 cases of immediate adverse reactions to amoxicillin–clavulanic acid. Skin test results with clavulanic acid were positive in both patients. Cahen and Wúthrich⁹ performed scratch tests and a skin prick test with clavulanic acid, both with positive results. González de Olano et al⁷ reported a patient with urticaria after receiving amoxicillin–clavulanic acid. The diagnosis resulted from a positive oral challenge result with amoxicillin–clavulanic acid and a negative challenge result with amoxicillin.

There are 3 reports of delayed reaction to clavulanic acid.^{8,10,12} Kamphof et al¹⁰ and Hoon Kim et al⁸ performed patch tests with clavulanic acid, and positive results were obtained in both cases.

Longo et al² described 2 patients with urticaria and angioedema after oral amoxicillin–clavulanic acid. The basophil activation test and sulphidoleukotriene release by basophils revealed a positive response with clavulanic acid.

During the last 5 years, we have observed an apparent increase in patients with suspected sensitization to clavulanic acid, probably because of the increasing use of amoxicillin associated with this drug over this period. Antibiotics containing clavulanic acid might be an increasing source of adverse reactions because of specific IgE to clavulanic acid. More studies with a larger number of patients are needed to support these conclusions.

Our report focuses on 9 patients who were given diagnoses of allergy to clavulanic acid. The diagnosis was made on the basis of the skin test and basophil activation test results with the clavulanic acid molecule.

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