

Drug allergy to the β -lactam antibiotics clavulanic acid and amoxicillin

ALLERGIC reactions to β -lactam antibiotics are well known. The common molecular structure is the β -lactam ring, which is linked to a second ring of varying structure. Side-chains can be linked to both rings (1). The immunogenicity of penicillins develops from the "major determinant" (penicilloyl) and the "minor determinants" (penicillin, penicilloate, penilloate) (2, 3). Preparations of the penicillin haptens are commercially available for skin testing (benzylpenicilloyl polylysine [PPL] and minor determinant mixture [MDM]).

Due to structural differences, penicillin haptens are not indistinguishably useful in the diagnosis of allergic reactions to related β -lactam antibiotics. Aminopenicillins differ in their side-chains. Cephalosporins and carbapenems (imipenem) differ in their second ring structure, as well as in side-chains. Therefore, variability of immunogenicity can be anticipated and has been observed clinically (1, 4, 5).

Clavulanic acid (clavam) is another β -lactam antibiotic. It develops only weak antibacterial activity, but can inhibit β -lactamases. In combination with amoxicillin, it is one of the most widely prescribed antibiotics. Clavulanic acid differs from penicillin in its second ring. It has a complex structure, breaking down into several haptenic groups. It was formerly judged to be of low immunogenicity (6). Only one report of two cases with a drug allergy to clavulanic acid has been published so far (7). We report an additional patient who presented an allergic reaction to a combination of amoxicillin and clavulanic acid.

■ Because of frontal sinusitis, a 27-year-old woman was treated with a combination of amoxicillin and clavulanic acid (Augmentin®). After 1 week's treatment, she developed an immediate-type allergic reaction with generalized, pruritic urticaria, facial edema (Quincke's), and dyspnea. The findings were confirmed by a dermatologist when she presented herself at the emergency department. Antibiotics were discontinued and treatment was initiated with steroids (50 mg prednisone p.o., 100 mg prednisolone i.v.) and an antihistamine (clemastine 1 mg i.v.). After discharge, the rash faded. Three days later, a pruritic rash of different appearance erupted again. The dermatologist diagnosed drug-induced exanthema, and treatment with steroids and antihis-

tamines was extended. Two days later, arthritic pain in hands and knees developed and persisted for 3 weeks.

■ Skin prick and intracutaneous testing was performed for penicillins, using the major determinant (PPL, Allergopen) and minor determinant mixture (benzylpenicillin and benzylpenicilloate, Allergopen) with negative results after 20 min, 24 h, and 48 h, respectively. The scratch test performed with amoxicillin (Clamoxyl®) was negative also, but the combination of amoxicillin and clavulanic acid (Augmentin) produced a clearly positive result (wheal ≥ 7 mm). To rule out an allergic reaction to clavulanic acid, pure substance (10 mg/ml) was obtained (SmithKline Beecham AG, Thörishaus, Switzerland), resulting in a positive prick test (wheal ≥ 5 mm). Three nonallergic controls did not react to either clavulanic acid or amoxicillin. The histamine-release test

(HRT) could not be interpreted, as the patient turned out to be a nonresponder to anti-IgE. Fernandez-Rivas et al. (7) described the same

Clavulanic acid can elicit an immediate-type allergic reaction.

problem in one patient and a positive HRT in another. They additionally examined RAST responses, but obtained negative results in both patients.

Epicutaneous patch tests for delayed-type hypersensitivity remained negative with penicillin and amoxicillin, whereas the lymphocyte stimulation test (LTT) revealed distinct stimulation indices for amoxicillin (SI=4.40) and only weak stimulation for clavulanic acid (SI=2.60) (Prof. W. Pichler, Institute for Immunology and Allergy, Inselspital Bern, Switzerland).

■ From our results, we concluded that primarily an IgE-mediated drug allergy to clavulanic acid had taken place. This is reflected by clinical history and the immediate positive reaction in skin tests. The second rash and the following arthritic episode were probably due to amoxicillin, as reflected by the positive LTT, and not IgE-mediated.

We conclude that the assessment of allergic reactions to the widely used combination of amoxicillin and clavulanic acid should include separate testing of the two compounds. This procedure may detect further drug allergies to clavulanic acid otherwise assigned to amoxicillin.

Key words: adverse effect; allergy; antibiotic; β -lactam; clavulanic acid; drug; hypersensitivity; penicillin.

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Anaphylactic reaction to hydroxycobalamin

IT IS WELL known that vitamin B₁₂ (vit. B₁₂) is often prescribed but seldom needed. On the other hand, if there is a real need, it is frequently for lifelong therapy. We must also remember that this is not a risk-free treatment, and severe allergic reactions are sometimes observed, even after several years of therapy (1).

■ A 54-year-old white man with a clinical and laboratory diagnosis of pernicious anemia was receiving hydroxycobalamin (HC) 5000 µg every 3 months. Twenty minutes after the sixth injection of HC, he had generalized urticaria and angioedema, vomiting, tachycardia, and hypotension. No other drug had been administered in the preceding week. Anaphylaxis was successfully treated in the emergency room with subcutaneous epinephrine, intramuscular hydroxyzine, and intravenous prednisolone and normal saline. His past medical history did not reveal any previous significant drug adverse

reactions, nor did it suggest atopy. The family history was irrelevant.

■ We performed skin prick tests with two commercial preparations of injectable HC and one commercial preparation of injectable cyanocobalamin (CC). Histamine caused a wheal of 8 mm and HC wheals of 4 mm in diameter. Prick tests with CC, with the solvents for vit. B₁₂, with common aeroallergens, and with foods were all negative. Subsequently, we performed intradermal testing with HC and CC, starting at 1:10 000 dilution and with 10-fold progression. Significant positivity started at a concentration of 1:10 for both HC and CC preparations, although the latter caused a smaller wheal (5 mm with CC; 9 mm with HC). Intradermal tests with the solvents were negative. Both prick and intradermal tests with the same preparations were negative in two healthy volunteers.

■ We discussed the case with the patient's hematologist and, after obtaining the patient's written informed consent, decided to attempt a desensitization procedure, in order to allow a therapeutic regimen of 500-µg vit. B₁₂ 15/15 days, eventually adjusted according to hematologic values. On an inpatient basis, the desensitization protocol started with a 1:100 dilution in normal saline of the commercial preparation of CC (1000 µg/ml), progressing in twofold increments every 30 min, until the 500-µg dosage was reached (Table 1). No adverse reactions were observed, and the patient was discharged 6 h after the last injection.

In a hospital setting, we have administered 500 µg CC, every 2 weeks, without adverse reactions and with normal hematologic counts and serum vit. B₁₂ levels. The skin tests, repeated approximately 1 year after desensitization, showed disappearance of the reaction to HC in the skin prick test and reduction of the reaction to HC and CC in intradermal tests, which now showed positivity only at a 1:1 dilution, HC having a still larger wheal (7 mm) than CC (5 mm).

Successful desensitization to vitamin B₁₂ after anaphylaxis in patients with pernicious anemia.

Table 1. Desensitization procedure (10 i.m. injections at 30-min intervals)

1st dilution: 1:100 (10 µg/ml)	0.1 ml→0.2 ml→0.5 ml
2nd dilution: 1:10 (100 µg/ml)	0.1 ml→0.2 ml→0.4 ml→0.8 ml
3rd dilution: 1:1 (1000 µg/ml)	0.15 ml→0.25 ml→0.5 ml

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