

A case of allergic contact dermatitis to clavulanic acid

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ABSTRACT



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Article Text

Clavulanic acid is a β -lactam antibiotic with weak antibacterial activity, but it is a potent inhibitor of β -lactamases. In association with amoxicillin, it has great antimicrobial activity and is one of the most frequently prescribed antibiotics worldwide in medical practice (1). Despite the large use of the drug, only six reports of a drug allergy to clavulanic acid have been reported so far (1–6). We report a patient who presented with an allergic contact dermatitis to clavulanic acid. To the best of our knowledge, this is the first report of an allergic contact dermatitis to clavulanic acid.

Case Report



A 35-year-old nurse presented with pruritic, erythematous patches that affected both her hands and her forearms ([Fig. 1](#)). The skin lesions developed 2 days after she had contact with Augmentin[®] (mixture of amoxicillin/clavulanic acid; Ilsung pharmaceuticals, Seoul, Korea) dry syrup and distilled water. The eruption disappeared within a few days after the administration of oral antihistamines and topical corticosteroids. We performed patch tests with the Korean baseline series of contact allergens (Chemotechnique diagnostics, Tygelsjö, Sweden) and Augmentin dry syrup 10, 1, and 0.1 mg/ml in aq. Positive reactions were seen to Augmentin dry syrup at D2 and D4 readings ([Table 1](#)); the Korean baseline series were all negative.

Fig. 1. Erythematous patches on both hands and forearms.

[\[Normal View\]](#)

Table 1. Patch test results

| Substances | Concentrations (mg/ml aq.) | D2 | D4 |
|----------------------------------|----------------------------|----|----|
| Augmentin [®] dry syrup | 10 | + | + |
| | 1 | + | + |
| | 0.1 | + | ? |
| Clavulanic acid | 10 | ++ | ++ |

We obtained pure preparations of all constituents of Augmentin dry syrup including amoxicillin, clavulanic acid, and four flavours from the pharmaceutical company. We performed patch tests, and the only positive reaction was to clavulanic acid (10 mg/ml) at D2 (++) and D4 (++) . No controls were undertaken.

On the basis of her clinical history and the result of the patch tests, a diagnosis was made of allergic contact dermatitis to clavulanic acid. We recommended her to change work from the ward to the outpatient department to avoid contact with clavulanic acid; there has been no recurrence of her problem.

Discussion



Clavulanic acid was first described in 1976 as a product of the organism *Streptomyces clavuligerus* (7). It is a broad-spectrum β -lactamase inhibitor and widely used for antimicrobial therapy in association with β -lactam antibiotics. Clavulanic acid has been associated with very few allergic reactions, which may be explained by a very low allergenic potential. Edwards et al. (8) found that clavulanic acid had low immunogenic and allergenic potentials, which was attributed to its complex immunochemistry: the reaction of clavulanic acid with protein amino groups produces a heterogeneous conjugate with low epitope densities. To our knowledge, only six reports of allergy to clavulanic acid have been reported so far and the reported reactions are generalized urticaria, itching, dyspnoea, facial oedema, hypotension, and loss of consciousness (Table 2) (1–6). In the first article, two cases were described, and prick and intradermal tests were positive with clavulanic acid alone in both patients (1). In the second article, a scratch test with amoxicillin/clavulanic acid and a prick test with clavulanic acid alone were both positive (2). In the above two articles, the authors concluded that clavulanic acid can elicit an immediate-type allergic reaction. In the third article, patch tests were performed and a positive reaction was seen only to clavulanic acid (3). In the fourth article, intradermal tests and prick tests were all negative with amoxicillin/clavulanic acid and the allergic reaction was only proven by oral provocation tests (4). In the fifth article, oral provocation test with amoxicillin was negative, but prick test and patch test were positive with amoxicillin/clavulanic acid (5). In the sixth article, oral provocation test with amoxicillin was negative, but challenge with amoxicillin/clavulanic acid was positive (6). Most of the reactions described were because of an immediate-type allergic reaction. In our case, we observed an allergic contact dermatitis as a result of a delayed-type allergic reaction to clavulanic acid because localized skin reaction was seen only where she had contact with Augmentin dry syrup, and the patch tests to the individual constituents of Augmentin dry syrup showed positivity only to pure clavulanic acid itself. Several experimental data support that both the β -lactam core structure and its specific side chain are recognized by T-cell receptors in penicillin allergy (9, 10). Therefore, we suppose that the β -lactam core structure and/or the oxazolidine ring may be associated with the T-cell response in delayed-type allergic reaction to clavulanic acid.

Table 2. Literature review of the reported cases of drug allergy to clavulanic acid

| References | Sex/Age (years) | Clinical presentation | Onset | Positive skin tests |
|----------------------------|-----------------|---------------------------------------|--------|-----------------------|
| Fernandez-Rivas et al. (1) | M/16 | Generalized urticaria and dyspnoea | 40 min | Prick and intradermal |
| | F/15 | Generalized urticaria, facial oedema, | 60 min | |

| | | | | |
|--|-------|--|---------------|-------------------|
| | | hypotension, and loss of consciousness | | |
| Cahen et al. (2) | F/27 | Generalized urticaria, facial oedema, and dyspnoea | Not described | Scratch and prick |
| Kamphof et al. (3) | F/1.5 | Generalized urticaria | A few days | Patch |
| Raison-Peyron et al. (4) | F/28 | Generalized urticaria, facial oedema, and dyspnoea | 15 min | Oral provocation |
| Bonadonna et al. (5) | F/34 | Generalized itchy erythema | 2 days | Prick and patch |
| González de Olano et al. (6) | F/46 | Generalized urticaria | 30 min | Oral provocation |

We have found that clavulanic acid can induce allergic contact dermatitis by a probable delayed-type allergic reaction. Therefore, we suggest that the assessment of allergic contact dermatitis 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.

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