

Table 1. Food additives tested and provocative doses

Sodium benzoate (E211): 50, 200 mg
Sodium metabisulfite (E223): 10, 25 mg
Tartrazine (E102): 5, 10 mg
Erythrosine (E127): 5, 10 mg
Sodium glutamate (E621): 100, 200 mg
Sodium nitrate (E251): 10, 100 mg
Sorbic acid (E200): 50, 200 mg
Butylated hydroxyanisole (E320): 10, 50 mg

2 h after the last provocative dose under observation at the allergy center.

The patient developed systemic urticaria and angioedema of the lips and hands about 2 h after the administration of 10 mg of tartrazine. Symptoms were easily controlled by antihistamine therapy. All other substances were tolerated.

The labels of several brands of tuna canned in olive oil were scrutinized: none reported tartrazine among the ingredients. Nonetheless, the causative role of canned tuna was unequivocal in this patient, and true fish allergy was excluded by SPT and oral challenge with fresh tuna. A nonspecific reaction to tartrazine is possible but unlikely. Thus, the only reasonable explanation of these findings is that significant amounts of this azo dye are present (but not declared) in some commercial preparations of tuna canned in olive oil; in effect, fish is included among foods to which azo dyes and benzoates are often added (1). It remains unclear why all the episodes of angioedema followed the ingestion of canned tuna in this patient; differences in tartrazine content among various preserved foods, as well as the patient's alimentary habits, might explain this effect.

Food-additive intolerance should always be considered in patients who experience repeated episodes of urticaria/angioedema after the ingestion of specific commercial food preparations, even if these are generally considered additive-free.

Key words: food-additive intolerance; tartrazine.

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Accepted for publication 14 April 1998
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ALLERGY 1998;53:816-817

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Drug-induced papulovesicular exanthema

DELAYED skin reactions, such as maculopapular exanthema to penicillin antibiotics, are common (1). However, the pathogenesis of these skin eruptions is unknown. Histology and the positive lymphocyte transformation test (LTT) indicate an immunologic mechanism in most of these cases (2, 3). Here we report on a long-lasting, generalized papulovesicular skin reaction following skin testing with penicillin preparations.

A 68-year-old Caucasian housewife reported generalized exanthema after parenteral injection of penicillin G 29 years before, which persisted for several weeks, in spite of discontinuation of therapy. As she changed her doctor, she was sent to re-evaluate the state of her drug allergy.

Sequential skin tests (scratch followed by intradermal testing) using commercially available extracts (0.05 ml PPL [0.025 mg/ml] and 0.05 ml MDM [0.6 mg benzylpenicillin/ml, 0.5 mg di-natrium-benzylpenicilloate/ml], both Allergopharma, Reinbeck, Germany) were performed on the volar side of the forearms. Results were recorded 15 min after testing and compared to the positive (1 mg/ml histamine diphosphate) and negative controls (phosphate-buffered saline [PBS]). Because of negative results, scratch patch skin tests were performed with penicillin G (200 000 U/

ml PBS), amoxicillin (750 mg/ml PBS), and PBS in the same session. After removal of the patch tests 24 h later, erythematous induration was noted at the site of the intradermal injection of PPL and MDM solution and at the patch test sites of penicillin G and amoxicillin. Over the next 2 days, vesiculopapular exanthema developed, spreading

Generalized papulovesicular exanthema induced by skin testing with penicillin preparations: an antigen- independent, T-cell- mediated, reactive, autoimmune process?

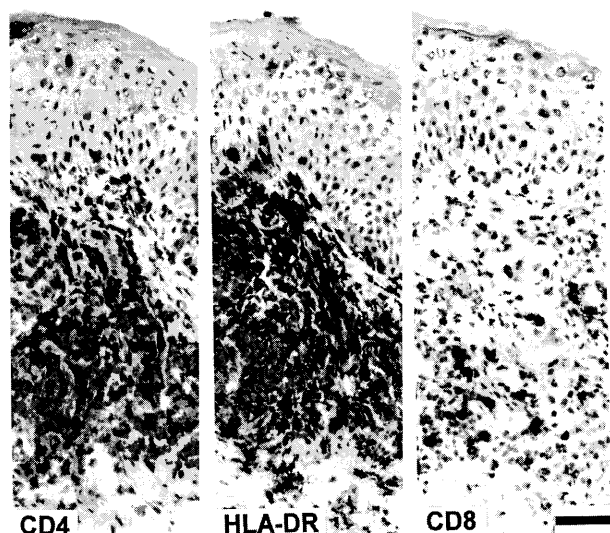


FIGURE 1 Immunohistochemical staining of consecutive sections of skin biopsy with antibodies against CD4, HLA-DR, and CD8 clearly demonstrate CD4⁺, HLA-DR⁺, CD8⁺ nature of infiltrating cells. Avidin-biotin complex/alkaline phosphate technique, developed with new fuchsin. Bar=0.50 μ m.

on both forearms and the back. A skin biopsy revealed spongiosis and inflammatory infiltration of predominantly CD4⁺, HLA-DR⁺ T cells in the upper dermis (Fig. 1). Clinical and laboratory investigations were normal and did not indicate neurologic or visceral involvement (ESR, hematology, liver, kidney, and urine analysis). The vesiculopapular exanthema persisted for 8 weeks with flare-up reactions if moderately exposed to sunlight. No specific IgE antibodies were detected to penicilloyl G and penicilloyl V (CAP FEIA, Pharmacia AB, Uppsala, Sweden). The LTT (3) revealed a strong proliferation to penicillin G (stimulation index [SI]: 66) and amoxicillin (SI: 16). One year later, the LTT was still positive (SI: 72 and 18, respectively). In four controls with exposure to penicillin antibiotics but no skin eruptions, the SI of the LTT was under 2.

This report of vesiculopapular exanthema following skin testing is peculiar for the following reasons.

Firstly, while generalized IgE-mediated reactions following skin testing are well known (4), our report demonstrates a reaction which was not IgE dependent but was probably T-cell dependent. It did not appear before 24 h, and it was not of the anaphylactic/urticarial type. Moreover, we failed to detect penicillin-specific IgE antibodies. Histologically, the skin was diffusely infiltrated by activated (HLA-DR⁺) CD4⁺ T cells. The LTT revealed a

strong T-cell response to penicillin G and amoxicillin with an unusually high proliferative response at the time of the reaction as well as after 1 year.

Secondly, the reaction was elicited by skin testing. It is unlikely that a substantial amount of penicillin determinants could have penetrated into the body tissue by skin testing. Usually, only a localized, delayed-type reaction is noted after patch tests, and we have never observed a generalized delayed reaction.

Thirdly, in spite of the long interval of 29 years between the initial drug allergy and skin testing, the patient showed an unusually strong reaction. This is hard to reconcile with the principle that an immune reaction decreases with time in the absence of an antigen.

A further astonishing finding was the long persistence of the reaction for approximately 3 months.

The pathogenesis of this generalized, persistent delayed-type skin reaction is difficult to explain by a simple antigen-dependent mechanism. The minute amounts of penicillin G or amoxicillin which penetrated into the body during skin testing may have stimulated T cells, which have an additional specificity against some autoantigenic determinants. These may be expressed preferentially during skin inflammation. Such a reactive autoimmune process might explain the generalized pattern elicited by a minute amount of antigen, the long time interval between primary exposure and the renewed symptoms, and the flare-up reactions following specific stimuli such as sun exposure (5).

Key words: autoimmunity; drug eruptions; drug hypersensitivity; patch tests; penicillin.

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Accepted for publication 17 April 1998

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ALLERGY 1998;53:817-818

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