

Case report

Positivity of patch tests in cutaneous reaction to diclofenac

Two case reports

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Immune-mediated reactions to NSAIDs are unusual. We have observed two cases of maculopapular eruptions occurring 48–72 h after administration of diclofenac sodium. Patch tests performed with diclofenac were positive. The histopathologic findings resembled those of contact dermatitis with different degrees of dermal involvement. Clinical, allergologic, and histopathologic patterns strongly suggest a type IV mechanism of hypersensitivity. Patch tests play an important role in the assessment of possible immunologic mechanisms underlying cutaneous reactions to drugs.

Key words: diclofenac; hypersensitivity reaction; skin tests.

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Diclofenac sodium is a nonsteroidal anti-inflammatory derivative (NSAID) of phenylacetic acid. The drug has both analgesic and antipyretic effects and is generally well tolerated. The adverse effects most frequently observed are gastrointestinal (13), although hepatitis (in some cases, fatal) (7, 8), extramembranous glomerulitis, acute interstitial nephritis (6), and minimal-change glomerulopathy (10) have been reported. The drug can also cause immune-mediated hematologic disorders, such as agranulocytosis (12), hemolytic anemia (11), and thrombocytopenia (5), as well as cutaneous reactions, such as exanthema or rash, urticaria, erythema, and eczema (2).

We describe two cases of cutaneous adverse reactions to diclofenac sodium that may have been caused by delayed hypersensitivity to this drug.

spread, pruriginous, erythematous, maculopapular eruption that appeared 72 h after she had started therapy with diclofenac (Voltaren Retard®)*, 200 mg/d orally, for diffuse arthrosis. There was no family history of allergic disease, but the patient reported several previous episodes of angioedema involving the face and neck which had occurred 30 min–1 h after she had taken noramidopyrine (Novalgina®) or other unspecified NSAIDs. She also reported one previous episode of bronchitis with fever and bronchospasm.

Allergologic studies

Skin tests (prick and intradermal) with diclofenac and noramidopyrine were performed. Intradermal injection of diclofenac (0.05 ml of a solution con-

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Patient 1

A 42-year-old white woman was admitted to hospital for angioedema of the face and neck and a wide-

*One tablet of Voltaren Retard contains sodium salt of *o*-(2,6-dichlorophenyl)-amino-phenylacetic acid (= diclofenac sodium) (100 mg) and the following additives: sucrose, talc, magnesium stearate, silica precipitate, cetyl alcohol, polyvinylpyrrolidone, hydroxy-propyl-methylcellulose, iron oxide, polysorbate, and titanium dioxide.

taining 0.75 mg/ml) produced a mild positive reaction after 48 h (infiltrate and erythema 13 mm in diameter). Patch testing with 0.1 ml of a solution containing diclofenac 75 mg/ml produced a positive result after 48 and 72 h. Patch tests with the European Standard Series were negative.

Control intradermal and patch tests performed with the same concentration on eight volunteers (four of whom had previously taken diclofenac) were negative. The total serum IgE (determined by radioimmunoassay) was 27 KU/l. Oral challenge tests with the additives contained in Voltaren Retard and in the solution used for the patch test were negative.

Cutaneous biopsy of the patch-tested skin showed, as a distinctive feature, a scale-crust containing serum and parakeratosis. Mild spongiosis was present in the epidermis and in the follicular epithelium. In the dermis, dilation of the superficial vascular plexus and a perivascular infiltrate composed primarily of lymphocytes were observed. A few eosinophils and mastocytes were scattered among the collagen fibers.

Patient 2

A 50-year-old white woman with a history of cervical arthrosis was admitted to the emergency ward of the hospital for a widespread, pruriginous, erythematous, maculopapular eruption that had appeared on the second day of therapy with diclofenac suppositories (100 mg twice daily) (one Voltaren suppository contains diclofenac sodium 100 mg and solid semisynthetic glycerides 1900 mg). This eruption was followed by angioedema of the lips and eyelids. An identical reaction had occurred 1 month earlier; 48 h after the patient had taken diclofenac 100 mg orally. The personal and family histories were negative for allergic disease. Treatment with betamethasone, 8 mg orally, and dexchloropheniramine maleate, 10 mg orally, was prescribed, and the symptoms disappeared. However, when these drugs were withdrawn, the erythematous eruption reappeared, regressing again after another 2 d of the same therapy.

Allergologic studies

The prick test performed with a 0.75-mg/ml solution of diclofenac was negative, but intradermal injection of 0.05 ml of the same solution resulted in a positive reaction after 36 h (erythema and infiltrate 2 cm in diameter). The patch test performed with 0.1 ml of a solution containing diclofenac 75 mg/ml produced a positive result after 48 and 72 h. Patch tests performed with the European Standard Series were negative. Oral challenge tests with the additives con-

tained in the Voltaren suppository and in the solution used for the patch test were negative.

Cutaneous biopsy of the patch-tested skin showed epidermal spongiosis with lymphocytic exocytosis and edema of the papillary dermis. In the dermis, there was a lymphocytic perivascular infiltrate around the superficial and deep plexus. Eosinophils and mastocytes were interspersed among the collagen fibers (Fig. 1). The total serum IgE level, determined by radioimmunoassay, was 10 KU/l.

Discussion

Allergy-like effects are produced by many nonsteroidal anti-inflammatory drugs, generally without any evidence of hypersensitivity (14). Patch tests, which are useful in the diagnosis of contact dermatitis caused by drugs (e.g., in pharmaceutical factory workers), are rarely positive in systemic adverse drug reactions (4). However, a role for patch tests has been recently suggested in drug-induced maculopapular eruptions (1, 3, 9).

The histopathologic findings observed in our patients were similar to most of those seen in contact dermatitis, ranging from superficial involvement of epidermis (patient 1) to a deeper extension into the dermis (patient 2) that is unusual in contact dermatitis. This pattern, while not diagnostic in itself, strongly suggests a type IV mechanism of hypersensitivity when associated with a delayed-onset cutaneous eruption and patch-test positivity. In patient 1, the history of a previous pseudoallergic reaction to noramidopyrine should also be emphasized.

Adverse reactions to NSAIDs are usually pseudoallergic, but there is increasing evidence that

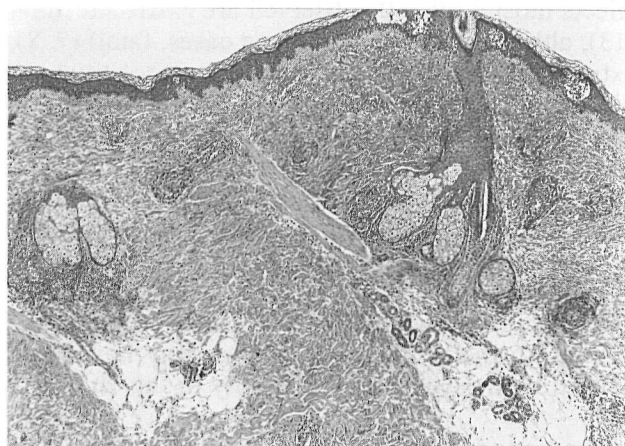


Fig. 1. Biopsy of patch-tested skin showing epidermal spongiosis with lymphocytic exocytosis and edema of papillary dermis. Lymphocytic perivascular infiltrate can be seen around superficial and deep plexus within dermis. Eosinophils and mastocytes are scattered among collagen fibers.

patients with these reactions must also be carefully evaluated for allergic mechanisms, which can be revealed with simple patch tests.

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