

Delayed hypersensitivity to diclofenac: a report on two cases

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Background: Although skin reactions have been reported during use of diclofenac, a nonsteroidal anti-inflammatory drug, immunopathogenic mechanisms have been demonstrated in only a few cases.

Methods: We administered skin and patch tests to two subjects who had developed maculopapular rashes respectively 48 and 72 hours after initiation of treatment with diclofenac.

Results: In both cases, prick and intradermal tests with the drug were negative at 20 minutes, but 24 hours later an erythematous infiltrate had appeared at the intradermal test site. Patch tests with diclofenac were also positive at 48 and 72 hours.

Conclusions: The features of both these cases are suggestive of delayed hypersensitivity to diclofenac. Delayed-reading intradermal and patch tests may be a simple and effective means of diagnosing reactions of this type.

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INTRODUCTION

Diclofenac, a nonsteroidal anti-inflammatory drug, is a phenylacetic-derivative that is generally well tolerated, although adverse reactions have been reported. Most are relatively benign gastrointestinal disturbances,¹ but there have also been reports of hepatitis (in some cases fatal)^{2,3} and various forms of renal damage.^{4,5} Diclofenac has also been associated with immune-mediated hematologic disorders, such as agranulocytosis,⁶ haemolytic anaemia,⁷ and thrombocytopenia.⁸ In addition, anaphylactoid^{9–11} and skin reactions (eg, exanthema, urticaria, erythema, and eczema)¹² have been linked to this drug. In some of these cases delayed hypersensitivity to topical^{13,14} or systemically administered^{15,16} diclofenac has also been documented.

This report describes two cases of delayed reactivity to diclofenac mani-

fested by maculopapular rashes, and constitutes an extension of our previous observations.¹⁶

PATIENTS AND METHODS

Case 1

Diclofenac tablets (Voltaren Retard, Ciba-Geigy, Origgio, Italy) were prescribed to a 66-year-old woman for pain associated with osteoarthritis. Forty-eight hours after taking the first 100-mg tablet, the patient developed a generalized pruritic maculopapular rash. Treatment was immediately interrupted, and the rash resolved after 7 days of corticosteroid therapy (6-methylprednisolone IV: 40 mg/day for three days, followed by 20 mg/day for four days).

There was no personal or family history of allergy. The patient claimed that she had used the same drug without any adverse effects during a similar bout of pain 2 months prior to the reactive episode.

One year after the reaction, prick and intradermal tests with diclofenac (0.75 mg/mL in 0.9% NaCl) were administered with negative results at 20 minutes. The intradermal test was per-

formed with 0.02 mL of the drug solution.

Thirty-six hours after the intradermal test, however, there was an erythematous infiltrate 10 mm in diameter. Patch testing was performed with 0.05 mL of a solution containing diclofenac 75 mg/mL in 0.9% NaCl and with the European Standard Allergen Series. Normal saline was used as a negative control. All reagents were applied to uninvolved skin on the patient's back using acrylate adhesive strips with small plates attached for test allergens (Curatest, Lohmann GmbH & Co. KG, Neuwied, Germany). Occlusion time was 48 hours. Readings were made according to the recommendations of Wilkinson et al,¹⁷ 15 minutes after removal of the strips and 24 hours later. The diclofenac solution produced a positive reaction (+) consisting of an indurated, erythematous lesion 15 mm in diameter, which was present at the 48-hour and 72-hour readings. No reactions were observed with the European Standard Series. The patient did not experience any adverse reactions to oral challenges with the additives contained in the Voltaren Retard tablet (sucrose, talc, magnesium stearate, silica precipitate, cetyl alcohol, polyvinylpyrrolidone, hydroxy-propyl-methylcellulose, iron oxide, polysorbate, and titanium dioxide). Control intradermal and patch tests with diclofenac (administered in the same manner) produced negative results in ten healthy volunteers, five of whom had previously used the drug.

Case 2

A 50-year-old woman experienced a pruritic maculopapular rash on the third day of diclofenac therapy (Voltaren suppository, 100 mg BID) for sciatica. Two days later the exan-

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them displayed a confluence of the original lesions, and facial edema appeared. At this point, the drug was discontinued, and betamethasone was started (4 mg IM BID). After 10 days of treatment, the eruption and edema had completely subsided. Both her personal and family histories were negative for allergy. Prior to the reactive episode, the patient had reportedly tolerated the same drug (Voltaren suppositories, sustained-release tablets and intramuscular injections) on various occasions.

The allergologic work-up was performed (as described above) 10 months after the above reaction. Prick and intradermal tests were negative at the 20-minute reading, but after 24 hours the latter had become positive, with an indurated, erythematous infiltrate measuring 15 mm in diameter. Patch testing produced an erythematous infiltrate (18 mm) with vesicles, which was present at the 48-hour and 72-hour readings.

Patch tests with the European Standard Allergen Series were negative.

Oral challenges with the additives contained in the Voltaren suppository (solid semisynthetic glycerides) were negative.

DISCUSSION

The majority of urticarial and/or angioedematous reactions to nonsteroidal anti-inflammatory drugs appear to be pseudoallergic phenomena, but there is evidence that maculopapular rashes occurring during use of these drugs may well be manifestations of cell-mediated hypersensitivity.^{15,16,18,19} Patch testing is most commonly used to diagnose contact dermatitis, which is one of the most typical manifestations of cell-mediated reactivity. We have found that this approach can also be useful in the work-up of maculopapular reactions to a variety of systemically administered drugs, including aminopenicillins,²⁰ diltiazem,²¹ and streptokinase.²² In these cases, biopsies of the patch-tested skin revealed perivascular lymphocyte-eosinophil infiltrates and epidermal spongiosis like those seen in allergic contact dermatitis. In-

tradermal testing generally produced an indurated wheal that appeared more than 8 hours after injection. In all of the 19 patients who agreed to submit to challenges with the suspect drug, positive reactions fully confirmed our skin-test and patch-test findings.^{20,22}

Over the last 3 years, we have used patch and/or intradermal tests with late readings to diagnose delayed hypersensitivity to the nonsteroidal anti-inflammatory drug flurbiprofen¹⁹ and diclofenac itself.¹⁶ The clinical characteristics of the two cases described in the latter report were quite similar to these presented here. Biopsies of the patch-tested skin again revealed features similar to those seen in allergic contact dermatitis.

As in the two previously described cases, the hypothesis of type IV (cell-mediated) pathogenic mechanism is strongly supported in the present ones by the delay of 48 hours or more between initiation of treatment and appearance of the rash, as well as by the patch-test and delayed intradermal reactions to diclofenac.

The possibility of an allergic mechanism should always be considered in patients who develop a rash during diclofenac therapy, and delayed-reading skin and patch tests may be a simple and effective means of diagnosing these cases.

REFERENCES

- O'Brien WM. Adverse reactions to nonsteroidal anti-inflammatory drugs. Diclofenac compared with other nonsteroidal anti-inflammatory drugs. *Am J Med* 1986;80(suppl. 48):70-80.
- Helfgott SM, Sandberg-Cook J, Zakim D, Nestler J. Diclofenac-associated hepatotoxicity. *JAMA* 1990;264:2660-2.
- Ouellette GS, Slitzky BE, Gates JA, et al. Reversible hepatitis associated with diclofenac. *J Clin Gastroenterol* 1991;13:205-10.
- Oliver Rotellar JA, Garcia Ruiz C, Martinez Vea A, Carreras Plana M. Minimal-change glomerulopathy associated with diclofenac: response to prednisone. *Am J Kidney Dis* 1989;14:530-2.
- Garrouste O, Bauwens M, Touchard G, et al. Glomérulite extra-membraneuse et néphrite interstitielle aiguë après prise de diclofénac. *Ann Med Interne* 1990;141:627-8.
- Salama A, Schutz B, Kiefel V, et al. Immune-mediated agranulocytosis related to drugs and their metabolites: mode of sensitization and heterogeneity of antibodies. *Br J Haematol* 1989;72:127-32.
- Salama A, Götsche B, Mueller-Eckhardt C. Autoantibodies and drug- or metabolite-dependent antibodies in patients with diclofenac-induced immune haemolysis. *Br J Haematol* 1991;77:546-9.
- Epstein M, Vickars L, Stein H. Diclofenac induced immune thrombocytopenia. *J Rheumatol* 1990;17:1403-4.
- Alkhawajah AM, Eifawal M, Mahmoud SF. Fatal anaphylactic reaction to diclofenac. *Forensic Sci Int* 1993;60:107-10.
- Milman U, Hermoni D. Anaphylactic reaction to oral diclofenac sodium sustained-release tablet. *Isr J Med Sci* 1994;30:909-10.
- Van Der Klauw MM, Wilson JHP, Stricker BHCH. Drug-associated anaphylaxis: 20 years of reporting in the Netherlands (1974-1994) and review of the literature. *Clin Exp Allergy* 1996;26:1355-63.
- Ciucci AG. A review of spontaneously reported adverse drug reactions with diclofenac sodium (Voltarol®). *Rheumatol Rehabil Suppl* 1979;2:116-21.
- Gebhardt M, Reuter A, Knopf B. Allergic contact dermatitis from topical diclofenac. *Contact Dermatitis* 1994;30:183-4.
- Gonzalo MA, Revenga F. Multiple cutaneous sensitization to nonsteroidal anti-inflammatory drugs. *Dermatology* 1996;193:59-60.
- Schiavino D, Papa G, Nucera E, et al. Delayed allergy to diclofenac. *Contact Dermatitis* 1992;26:357-8.
- Romano A, Pietrantonio F, Di Fonso M, et al. Positivity of patch tests in cutaneous reaction to diclofenac. *Allergy* 1994;49:57-9.
- Wilkinson DS, Fregert S, Magnusson B, et al. Terminology of contact dermatitis. *Acta Dermatovener* 1970;50:287-92.
- Ibañez MD, Alonso E, Muñoz MC, et al. Delayed hypersensitivity reaction to paracetamol (acetaminophen). *Allergy* 1996;51:121-3.
- Romano A, Pietrantonio F. Delayed

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- hypersensitivity to flurbiprofen. *J Intern Med* 1997;241:81-3.
20. Romano A, Di Fonso M, Papa G, et al. Evaluation of adverse cutaneous reactions to aminopenicillins with emphasis on those manifested by maculopapular rashes. *Allergy* 1995;50:113-8.
21. Romano A, Pietrantonio F, Garcovich A, et al. Delayed hypersensitivity to diltiazem in two patients. *Ann Allergy* 1992;69:31-2.
22. Romano A, Di Fonso M, Mormile F, et al. Accelerated cell-mediated broncho-obstructive reaction to inhaled stepronin: a case report. *Allergy* 1996; 51:269-71.
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