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# Fixed drug eruption to piroxicam. Positive patch tests with cross-sensitivity to tenoxicam

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**In our experience, fixed drug eruption (FDE) is not a rare example of cutaneous adverse drug reactions, but the identification of the drug responsible often remains a challenge. We report on a patient in whom piroxicam was identified as the cause of recurring lesions of FDE. Epicutaneous testing with the offending drug was positive on residual lesions, but not on uninvolved skin. Histopathological and immunohistochemical findings on the positive tests were identical to those in an**

**acute lesion of FDE. Patch testing on lesional skin revealed cross-sensitivity between piroxicam and tenoxicam, but no reactivity to thiosalicylic acid. This suggests that the molecular moiety involved in FDE to piroxicam is shared by tenoxicam, in contrast to piroxicam photosensitivity where there is no cross-reaction between these two drugs and the offending moiety is antigenically and structurally similar to thiosalicylic acid.** (*J Dermatol Treat* (1999) 10:209–212)

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## Case report

A 55-year-old woman had suffered four recurrent attacks in 8 months, consisting of painful, erythematous and oedematous 2 to 8 cm patches, localized on the trunk, buttocks and thighs. In each outbreak of cutaneous lesions, previously involved sites were affected as well as new ones. Acute lesions resolved spontaneously to bluish-brown round patches, typical of a fixed drug eruption (FDE). Although she was being treated chronically with several drugs, drug history for FDE was unrewarding. Patch testing was performed on residual lesions with the patient's usual medication (diclofenac, nabumetone, thiocolchicoside and anti-glaucoma eye drops) and, on uninvolved skin, with these drugs, with the Portuguese Contact Dermatitis Group Standard Series (which includes thiosalicylic acid 0.1% in petrolatum) and with a nonsteroidal anti-inflammatory series (indomethacin, tenoxicam, diclofenac, fentiazac, naproxen, piroxicam, phenylbutazone, flurbi-

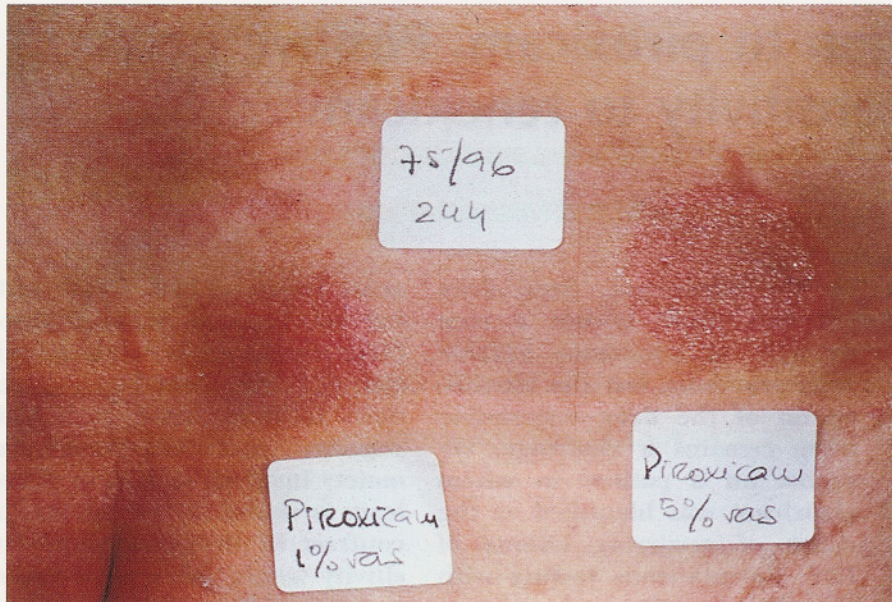
profen, etophenamate, bufexamac and azapropazone). All these tests were negative.

Six months later, advised to pay attention to all drugs used, she reported a new outbreak of acute FDE lesions 24 h after taking a 20-mg tablet of piroxicam. She then recalled having occasionally taken this NSAID that was part of her husband's medication. A month later, patch tests were performed on involved skin with piroxicam (1% and 5% in petrolatum), tenoxicam (5% in petrolatum) and thiosalicylic acid (0.1% in petrolatum). At 24 and 48 h, tests with piroxicam and tenoxicam were positive (Figure 1), with a violaceous papular erythema, similar to the patient's acute FDE lesions, whereas patch testing with these drugs on normal uninvolved skin was negative. Thiosalicylic acid was negative in both involved and uninvolved skin.

Histopathology of an acute lesion of FDE and of the positive tests at 24 and 48 h, showed, in all three specimens, typical findings of FDE, with intense hydropic degeneration of basal cells, dyskeratotic keratinocytes, scattered mononuclear cells in the epidermis, pigmentary incontinence, marked dermal papillary oedema with subepidermal bullae, vascular dilatation and a perivascular mononuclear cell infiltrate. On immunohistochemistry, performed on formaldehyde-

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**Figure 1**

Positive patch test reaction to piroxicam at 1 and 5% in petrolatum on a residual lesion of FDE

fixed samples, there was staining for HLA-DR in both the dermis and the epidermis with a striking positivity around keratinocytes. There was a similar staining for CD4 and CD8 on the dermal infiltrate, with scattered CD4<sup>+</sup> and CD8<sup>+</sup> exocytotic cells in the epidermis.

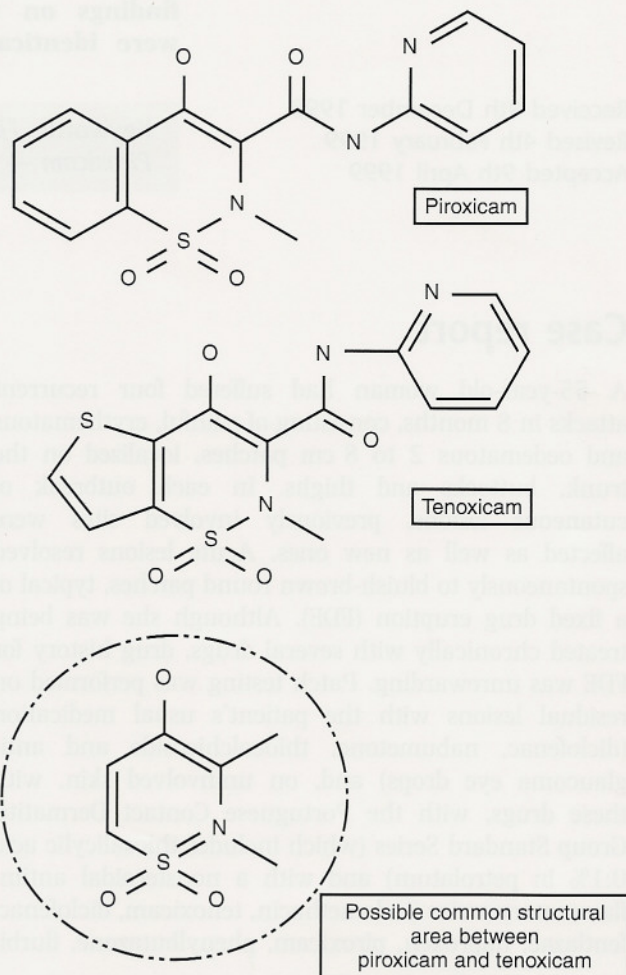
The patient did not have a recurrence of FDE after being advised not to take piroxicam or tenoxicam.

## Discussion

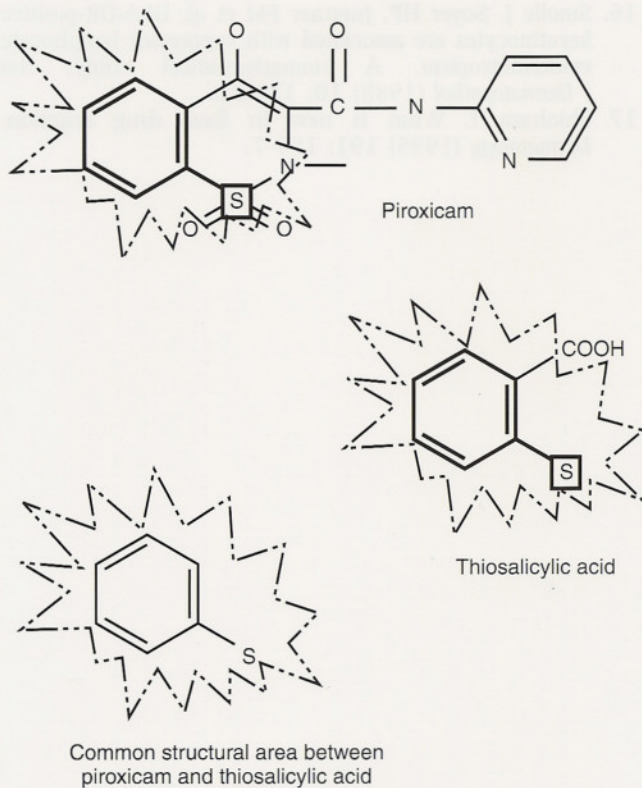
Although there are only six published cases of FDE due to piroxicam,<sup>1-5</sup> this is not, in our experience, a rare adverse effect of this drug.

Since the early 1960s, epicutaneous testing on residual lesions has been used as a diagnostic tool for the identification of the causative drug in FDE,<sup>6</sup> with irregular results. In two large series, Alanko et al obtained positive open epicutaneous tests in 44 out of 54 patients, with positive reactions in all of the 25 patients with FDE due to phenazone salicylate.<sup>7,8</sup> When positive, topical provocation is a reliable method for identifying the causative drug in FDE and can replace oral challenge with advantage, but a negative test cannot be validated.

Piroxicam has previously been tested epicutaneously in four patients with FDE, all with positive results,<sup>2-5</sup> and in two of them with cross-reaction with tenoxicam and droxicam, the prodrug of piroxicam.<sup>4,5</sup> Thiosalicylic acid was negative in the single patient tested.<sup>4</sup> These findings are coincident with ours, with cross-sensitivity between piroxicam and tenoxicam and no cross-reactivity with thiosalicylic acid, suggesting that piroxicam and tenoxicam, but not thiosalicylic acid,

**Figure 2**

Chemical structures of tenoxicam and piroxicam, also indicating a common structural area between the two drugs



**Figure 3**

Chemical structure of piroxicam and thiosalicylic acid. These molecules have in common a benzene ring with an attached sulphur atom, which in piroxicam is "buried" within the adjoining ring

have a common moiety (Figure 2) that is involved in the FDE.

On the other hand, in photosensitivity to piroxicam, patients do not cross-react with tenoxicam,<sup>9</sup> as piroxicam seems to be photodegraded by UVA into a thiosalicylate portion, antigenically and structurally

very similar to thiosalicylic acid as reported by Gonçalo et al (Figure 3).<sup>9-11</sup> So, whereas patients with FDE to piroxicam should not be treated with tenoxicam, the latter drug has been shown to be safe in patients with photosensitivity to piroxicam.<sup>9</sup>

Histopathology, performed on the positive tests did not show the usual features of an allergic contact dermatitis but showed the typical features of an acute FDE, namely basal cell vacuolization, keratinocyte necrosis and subepidermal bullae. On immunohistochemistry, there was a similar staining for CD4 and CD8 on the dermal inflammatory infiltrate, confirming previous reports.<sup>12,13</sup> Scattered exocytotic CD4<sup>+</sup> and CD8<sup>+</sup> cells were seen in the epidermis and, although double staining was not performed, CD8<sup>+</sup> cells were apparently over-represented, in accordance with a probable major role of these cells in FDE.<sup>14</sup> Strongly HLA-DR<sup>+</sup> keratinocytes have been previously observed by Hindsén et al in two patients with acute FDE.<sup>12</sup> This association of HLA-DR<sup>+</sup> keratinocytes with CD8<sup>+</sup> lymphocyte epidermotropism has been found by Smolle et al.<sup>15,16</sup> As an alternative explanation, the direct activation of a subset of keratinocytes by the causative drug, independent of the presence of antigen-specific T cells, could induce keratinocyte HLA-DR expression as an earlier event in FDE.<sup>17</sup>

Performing patch testing and studying its clinical, temporal and histopathological characteristics, which in our case were similar to the skin reaction itself, may also bring some insight into the pathogenesis of FDE. This very probably involves an immune hypersensitivity reaction, although different in those aspects from the allergic contact dermatitis reaction. This clinical case is a good demonstration that different cutaneous adverse reactions to the same drug can have various pathogenic mechanisms, with different clinical implications.

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Figure 1  
Chemical structure of phenolphthalein and its lactone form. The lactone form is formed in acidic conditions, while the open form is formed in basic conditions. The lactone form is the active form of the drug.

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