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Topical Provocation in Fixed Drug Eruption from Nonsteroidal Anti-Inflammatory Drugs

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Key Words

Drug eruption · Fixed drug eruption · Topical provocation · Lesional patch testing · Nonsteroidal anti-inflammatory drugs (NSAID) · Feprazone · Nimesulide · Piroxicam · Tenoxicam

Abstract

Objective: Evaluate the importance of topical lesional provocation in the study of fixed drug eruption (FDE) from nonsteroidal anti-inflammatory drugs (NSAID). ***Patients and Results:*** We studied 14 patients with FDE imputed with high probability to piroxicam (8 patients), nimesulide (5) and feprazone (1). One patient with FDE from piroxicam suffered lesion reactivation after intravenous tenoxicam. The suspected drug and related compounds were patch tested on residual lesional skin and on the normal back skin. Positive results were obtained, only in affected areas, in 13 out of 14 patients (92.9%): in all cases due to feprazone and nimesulide and in 7/8 cases of FDE due to piroxicam. The 7 patients reactive to piroxicam also had positive tests to tenoxicam, and 1 out of 5 reacted to meloxicam. None reacted to thiosalicylic acid. ***Comments and Conclusions:*** Topical lesional provocation is a safe, sensible and specific complementary method for drug imputation in FDE from these NSAID, namely for nimesulide, as it reproduced a positive test in the 5 patients. In the case of FDE from piroxicam, our studies confirm cross-reactivity with tenoxicam whereas in piroxicam-induced photosensitivity tenoxicam can be used safely. In photosensitivity the responsible moiety is a UVA photoproduct of piroxicam antigenically and structurally similar to thiosalicylic acid, a moiety which is not involved in FDE.

Introduction

The list of drugs inducing fixed drug eruption (FDE) is very extensive, with temporal and regional variations reflecting mostly different prescription attitudes [1–3]. Phenazone salicylate, barbiturates and tetracyclines, the main drugs responsible for FDE a few decades ago [1, 4, 5], have largely been outnumbered by cotrimoxazole [2, 3] and nonsteroidal anti-inflammatory drugs (NSAID), as in our experience [6, 7].

Drug imputability in this cutaneous adverse drug reaction (CADR) can be difficult, namely in patients on multiple drugs. Oral reintroduction performed after the refractory period can be considered the standard test, even though it is time consuming and may induce new lesions,

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Table 1. Characteristics of the patients and the lesions of FDE induced by NSAID

Drug	Sex	Age years	Number of lesions	Clinical aspect	Recurrences	Associated drugs	Reintroduction	Imputability score
FPZ	M	16	3	oedema	2	no	+	I4
NIM1	M	32	3	oedema + vesicles	1	yes	n.d.	I3
NIM2	F	21	2	oedema + papules	2	no	+	I4
NIM3	F	32	2	bullae	2	no	+	I4
NIM4	F	36	1	oedema + bullae	2	no	+	I4
NIM5	F	43	2	oedema + bullae	2	no	+	I4
PRX1	F	20	3	oedema	3	yes	?	I3
PRX2	F	70	3	oedema	3	yes	+	I4
PRX3	M	56	4	oedema + vesicles	3	no	+	I4
PRX4	F	61	5	oedema	3	yes	+	I4
PRX5	M	53	>10	oedema	>4	no	+	I4
PRX6	F	55	>15	oedema	>4	no	+	I4
PRX7	F	78	>20	bullae	>4	yes	+	I4
PRX8/TNX	F	33	1	bullae	4	no	+	I4

FPZ = feprazone; NIM = nimesulide; PRX = piroxicam; TNX = tenoxicam; I3 = high intrinsic imputability score; I4 = very high intrinsic imputability score; n.d. = not done.

eventually with extensive lesional skin detachment [1–3]. Epicutaneous testing performed on residual lesions of FDE is often positive [3–7], but there are still many aspects of standardization in this procedure that have not been fulfilled, namely in the study of NSAID.

Patients and Methods

Patients

Between 1996 and 2000, we studied 14 patients (4 male/10 female) aged between 16 and 78 years (medium 43.3 years) with FDE attributed, according to the French Pharmacovigilance criteria [8], with a high or very high intrinsic probability (I3 or I4) to the following NSAID: feprazone (Zepelin™) – 1; piroxicam (Feldene™, Reumoxicam™ and/or Brexin™) – 8, and nimesulide (Nimed™, Aulin™ and/or Jabasulide™) – 5 (table 1).

Patients had one or more cutaneous lesions typical of FDE that resolved with residual macular hyperpigmentation. Lesions were widely distributed on the trunk, extremities or face, ranging from one single large round lesion (12 cm in diameter) to more than 20 lesions (from 1 to several centimeters in diameter). In the acute episode, lesions presented as erythematoedematous plaques (6 patients), with papules or vesicles (3 patients) or bullous detachment (5 patients), with no apparent relation between the intensity of skin detachment and the number of recurrences. Pathological confirmation by skin biopsy during the acute episode was performed in 5 cases. Apart from 1 patient, all referred 2 or more episodes of lesion reactivation, occasionally involving new areas. In the absence of a correct diagnosis, these lesions recurred within 6–48 h after involuntary reintroduction of an NSAID, taken sporadically and as an isolated drug in 9 patients (table 1).

Table 2. NSAID series used for patch testing

NSAID	Test concentration	Supplier
Tenoxicam	5% pet.	Roche
Piroxicam	5% pet.	Oftalder
Fentiazac	5% pet.	Oftalder
Diclofenac	5% pet.	Oftalder
Indometacin	5% pet.	Oftalder
Naproxen	5% pet.	Oftalder
Flurbiprofen	5% pet.	Oftalder
Phenylbutazone	5% pet.	Oftalder
Feprazone	5% pet.	Oftalder
Meloxicam	5 and 10% pet.	Boehringer-Ingelheim
Nimesulide	5 and 10% pet.	Rhône-Poulenc Rorer

Methods

Six to 8 weeks after the acute episode, we performed patch tests on the normal back skin with the Standard Test Series of the GPEDC (Grupo Português de Estudo das Dermatites de Contacto) and with a series of NSAID prepared at our hospital using the pure powder of the drug kindly supplied by the pharmaceutical industry or prepared by Oftalder, Produtos Farmacêuticos SA, for the GPEDC (table 2). The suspected NSAID and related molecules were also patch tested on the residual pigmented lesions of FDE, as follows: pure substances in petrolatum were applied with occlusion for 24 h (Finn chambers on Scampor tape; Epitest Ltd.), with one single patch or several patches separated by more than 3 cm in each residual lesion. Readings were performed on day 1 (within 30 min of patch removal) and

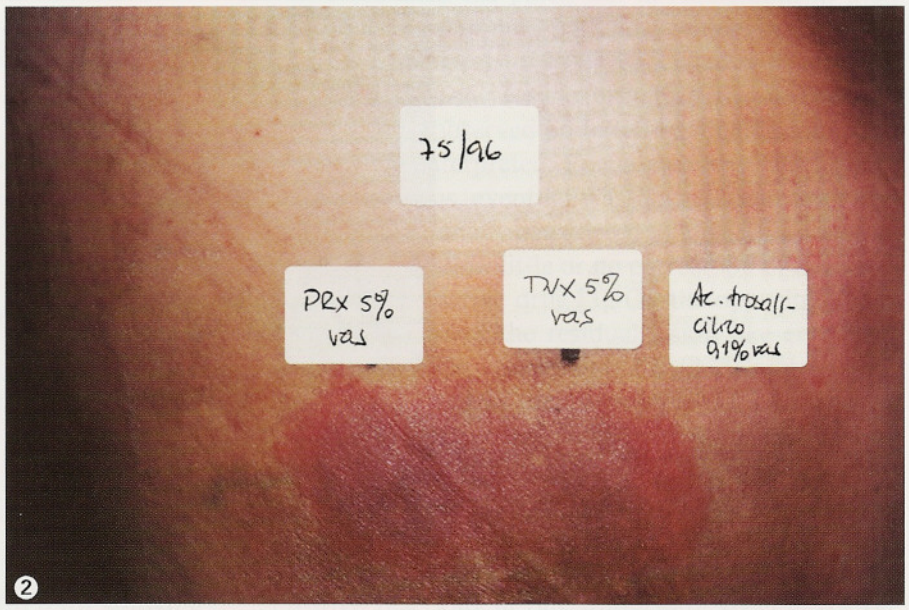

Fig. 1. Positive tests with 5 and 10% nimesulide in patient NIM3.
Fig. 2. Positive tests in a large residual lesion of FDE (patient PRX6) from piroxicam (PRX), with cross-reaction with tenoxicam (TNX) and no reaction to thiosalicylic acid.

on day 2 (24 h after patch removal). Tests were considered positive only if there were objective modifications of the residual lesion. Skin histology was performed in 4 positive tests.

As negative controls, apart from testing the NSAID on the normal back skin, we performed patch tests on residual lesions with white petrolatum (3 cases) and with NSAID that were not responsible in that particular case, namely nimesulide (4 cases), piroxicam (3 cases), tenoxicam (2 cases), naproxen (2 cases) and diclofenac (1 case).

Results

Tests with the suspected NSAID were positive in 13 patients (92.9%), with reactions occurring exclusively on the areas of the residual lesions. The single patient with FDE from feprazone as well as all 5 patients with FDE from nimesulide had positive reactions, with no significant difference between the 5 and 10% concentration used for testing nimesulide (fig. 1).

Piroxicam was positive in 7 of the 8 patients tested (87.5%) and all these 7 patients also reacted to tenoxicam

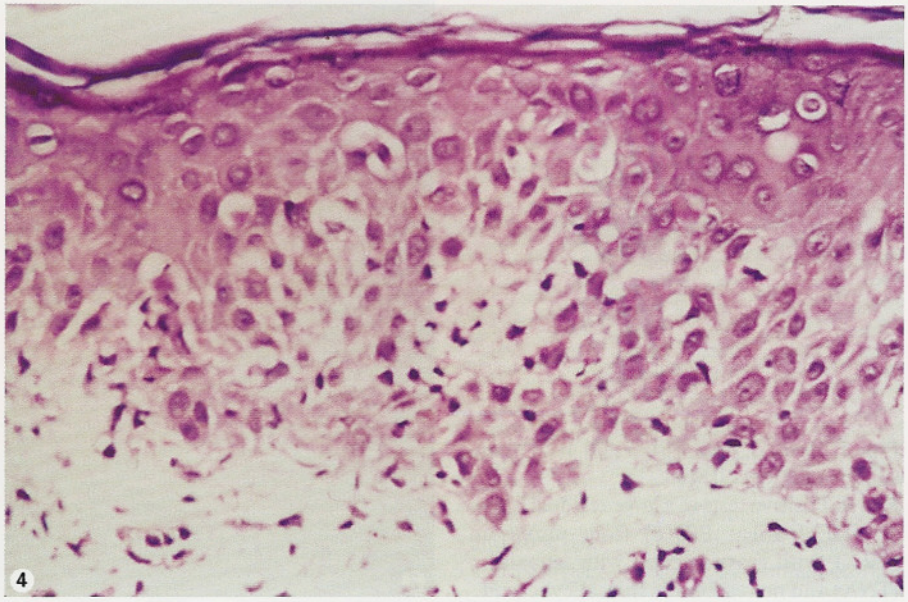

Fig. 3. Positive reaction to the three oxicams – piroxicam (PRX), tenoxicam (TNX) and meloxicam (MLX) – in the residual lesion of patient PRX8/TNX.
Fig. 4. Histology of a positive test reaction from piroxicam at 24 h (patient PRX6).

(fig. 2). Among 5 patients tested with meloxicam, 1 showed a positive reaction with the 10% concentration (fig. 3). Thiosalicylic acid at 0.1% pet. was negative in the 6 patients tested (fig. 2; table 3).

Morphological modifications induced by patch testing on the residual lesions were evident on day 1, with increasing intensity at the second reading in 3 patients and significant decreasing intensity in 1. They consisted of a pruriginous bright or violaceous erythema, present in all cases, associated with an edematous infiltration in 4 cases, papules in 1 case, vesicles in 4 cases and bullae in 2 cases, in most mimicking the reaction observed during the acute episode of FDE. Reactions were mainly limited to the area of patch application, but in 5 cases there was reactivation of the whole residual lesion tested, with skin detachment in 2 of these cases. There was neither reactivation of nontested lesions nor development of new lesions during skin testing.

Skin biopsy performed in 4 positive tests revealed hydropic degeneration of the basal layer, apoptotic keratinocytes, dermal perivascular lymphocytic infiltrate and pigment incontinence, associated with rare areas of lym-

Table 3. Test results with piroxicam and related compounds

	Piroxicam	Tenoxicam	Meloxicam	Thiosalicylic acid
PRX 1	–	–	–	–
PRX 2	+	+	–	–
PRX 3	+	++	n.t.	–
PRX 4	++	++	–	n.t.
PRX 5	++	++	n.t.	–
PRX 6	++	++	n.t.	–
PRX 7	++	++	–	–
PRX8/TNX	++	++	++	n.t.
Total	7/8	7/8	1/5	0/6

+ = Erythema and infiltration; ++ = erythema and papules or bullae, or infiltration of the whole residual lesion; n.t. = not tested.

phocyte exocytosis, spongiosis and intraepidermal vesicle formation (fig. 4).

Both control tests, those performed on the normal back skin and those performed with nonsuspected substances, were negative.

Positive results were validated by the absence of new recurrences after suspension of the causative NSAID and, in 3 patients also by an involuntary positive rechallenge. One patient with FDE from piroxicam developed lesional reactivation within 12 h of intravenous tenoxicam (Tilcotil™) administered in the postoperative period of an orthopedic surgery (patient PRX8/TNX; table 1).

Comments and Conclusions

Patch testing, which is well standardized for studying allergic contact dermatitis (ACD), is often useful in the diagnosis of the offending drug in FDE [3–7]. Nevertheless, as there are differences in the clinical and physiopathological aspects of these two entities, this technique has to be adapted to the study of FDE so that we can retrieve the most specific and sensitive results. Several aspects of the skin testing technique in residual lesions of FDE need special attention, namely one which considers the length of the refractory period we have to respect before testing, the ideal time for test reading (6, 24, 48 or 96 h) and the validation of the results, either accepting as a positive reaction only objective modifications or also subjective changes, like pruritus.

Although some authors did not respect a refractory period [3], in our experience, positive reactions were obtained 6–8 weeks after the last acute episode, as usually recommended for testing in drug eruptions [9]. With the use of open testing it is possible to follow the time course of the reaction and perform sequential readings [4]. Nevertheless, occlusion for 24 h may improve drug penetration and, even if the reaction develops within 6–18 h, it remains positive at 24 h, which we found to be a very adequate time for the reading. Later readings performed by several authors [3] did not increase the number of positive reactions in our study; there was only an increase in the intensity of the reaction in 3 cases whereas for 1 case the reaction decreased significantly. So, in FDE the 48-hour reading should not be the first, as in ACD, but it can be important in negative or doubtful reactions.

Apart from the time course, positive reactions in FDE are different from the patch test in ACD, both in their clinical aspect and in their pathology which, in our cases, showed typical aspects of FDE associated with intraepidermal spongiosis and vesicle formation (fig. 4). The multiform reactions observed on tested residual lesions have to be carefully interpreted. For instance, isolated symptoms, like pruritus, eventually associated with faint erythema, are occasionally considered as a positive reaction, although studies show little or no correlation of this reaction with the causative drug [3]. On the opposite, objective modifications of the residual lesion like erythema, infiltration, papules, vesicles or bullae [3–5], which in our experience occurred in the 13 positive patients, show a high degree of positive correlation with the causative drug [3]. Moreover, the clinical pattern of these positive tests was, in most cases, reproducing the reaction observed during the acute episode of FDE after systemic drug administration.

Positive reactions in our study were specific for the causative drug, as they were not observed with petrolatum or with nonrelated NSAID. In this group of substances patch testing on residual lesional skin showed a high sensitivity (92.9%), superior to other extensive studies involving more heterogeneous groups of drugs (81.5%) [3, 5]. We had no adverse events, namely reactivation of nontested residual lesions or development of new lesions, as occasionally occurs with systemic drug reintroduction [2].

Opposing the data from other countries [1–5], in our experience NSAID are frequently responsible for FDE [6, 7], namely nimesulide and oxicams that have ranked, respectively, first and third among NSAID consumption by our population in the last few years [10].

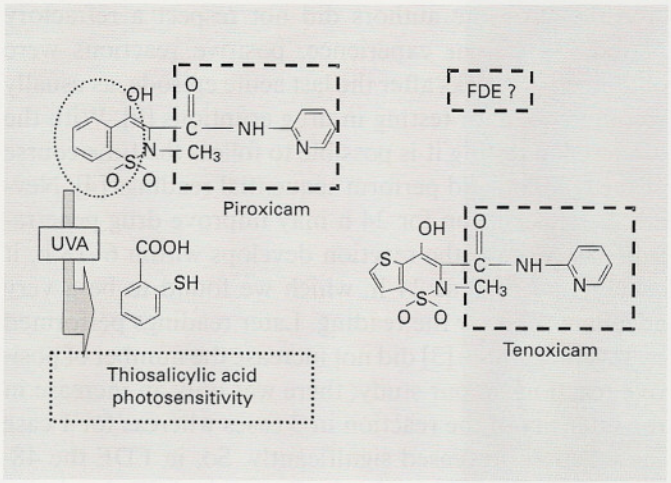

Fig. 5. Chemical formulas of the oxicams, piroxicam and tenoxicam, and thiosalicylic acid, with the indication of the moiety that is involved in piroxicam photosensitivity (·····) and the one probably involved in the FDE from oxicams (– – –).

There are few reports of FDE from nimesulide in the literature [11] and, if we exclude the 3 cases recently published by our group [7] that are included in this study, we found no reference to patch testing in this CADR to nimesulide, although this test seems to be very rewarding.

Isolated cases of FDE from piroxicam have been referred since 1989 [6, 12–16]. Local provocation was positive in 4 out of the 5 patients tested [6, 14–16] with cross-reaction to tenoxicam in all the 3 cases studied [6, 15, 16] and in our 7 patients. This is the most extensive study showing cross-reaction between these 2 oxicams in the patch test on residual lesions of FDE, which was corroborated, in 1 case, by involuntary tenoxicam administration with reactivation of the FDE originally induced by piroxicam. It is important to stress that this cross-reactivity cannot be extended to all CADR from piroxicam, namely for photosensitivity [17]. As we have shown, photosensitivity is due to a UVA photoproduct of piroxicam that is antigenically and structurally similar to thiosalicylic acid, which is not formed upon UVA irradiation of tenoxicam [17, 18]. In the case of FDE, the thiosalicylate moiety of piroxicam does not seem to be involved, as none of our 6 patients nor 2 other previously published cases reacted to thiosalicylic acid [6, 15] (fig. 5). Although we found no references, cross-reactions with other oxicams, namely meloxicam, may also occur in FDE from piroxicam, as we have shown in the patch test in 1 out of 5 cases studied.

In conclusion, patch testing in residual lesions as a local provocation of FDE is a safe procedure that can be used with high sensitivity and specificity as a complementary method for drug imputation in this CADR induced by these NSAID. In the particular case of piroxicam, skin testing was useful also to study the physiopathology of its cutaneous adverse effects.

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