



ORIGINAL ARTICLE

Piroxicam-induced fixed drug eruption: Cross-reactivity with meloxicam

Haifa Ben Romdhane | Helmi Ammar | Najeh Ben Fadhel | Zohra Chadli |
Nadia Ben Fredj | Naceur A. Boughattas | Amel Chaabane | Karim Aouam

Faculty of Medicine, Department of
Pharmacology, EPS Fattouma Bourguiba,
University of Monastir, Monastir, Tunisia

Correspondence

Dr Haifa Ben Romdhane, Faculty of Medicine
of Monastir, Department of Pharmacology,
Rue Avicenne, 5019 Monastir, Tunisia.
Email: haifabr@hotmail.com

Background: Non-steroidal anti-inflammatory drugs constitute a main cause of fixed drug eruption (FDE). A few cases of piroxicam-induced FDE have been reported; however, the cross-reactivity among oxicams has rarely been evaluated.

Objectives: To describe a series of patients with piroxicam-induced FDE, mostly confirmed by a positive patch test reaction, in whom cross-reactivity to meloxicam was assessed.

Methods: We included all cases of piroxicam-induced FDE diagnosed in the department of pharmacovigilance of Monastir. Patch tests for piroxicam and meloxicam were performed in the involved skin according to the European Network on Drug Allergy recommendations. Oral provocation tests (OPTs) were performed for patients with negative skin test results.

Results: Seven patients were included in this study. FDE was multiple for five patients and solitary for two. Bullous eruption was noticed in two cases. Lesional patch tests for piroxicam gave positive results in six patients. To assess cross-reactivity with meloxicam, this was patch tested. The test gave a positive result in only one patient. OPTs with meloxicam gave positive results in two patients with negative patch test results.

Conclusion: Meloxicam is not a safe alternative for the treatment of piroxicam-induced FDE, and OPTs can be used to confirm tolerance before this drug is prescribed as a safer alternative.

KEYWORDS

cross-reactions, fixed drug eruption, meloxicam, patch test, piroxicam

1 | INTRODUCTION

Fixed drug eruption (FDE) is a common cutaneous and/or mucosal lesion, characterized by the recurrence of single or multiple erythematous plaques that typically regress leaving residual hyperpigmentation. FDE follows repeated intake of the causative agent.¹ Fresh FDE lesions are well-defined, round or oval patches of redness and oedema of the skin; sometimes the whole lesion can be a blister.² The reaction varies in severity from a small localized lesion to generalized involvement. Recent research suggests a cell-mediated process that involves an antibody-dependent and cell-mediated cytotoxic response. CD8⁺ effector/memory T cells play an important role in reactivation of lesions with re-exposure to the offending agent.^{3,4} Several drugs have been associated with such cutaneous reactions, including

anticonvulsant agents, sulfonamides, paracetamol, and tetracyclines.⁵ Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most implicated drugs in the induction of FDE.⁵ Some cases of piroxicam-induced FDE have been reported. However, cross-reactivity among oxicams in cases of piroxicam-induced FDE has rarely been evaluated. We describe herein a series of patients with piroxicam-induced FDE, mostly confirmed by a positive patch test reaction, and in whom cross-reactivity with meloxicam was assessed with an appropriate allergy work-up.

2 | PATIENTS AND METHODS

We retrospectively included all cases of piroxicam-induced FDE diagnosed in the department of pharmacovigilance of Monastir during a

period of 13 years (2004–2017) as single or multiple erythematous plaques that regress, leaving residual hyperpigmentation. The assessment of the causal relationship between piroxicam and FDE was established according to the Naranjo scale.⁶ We collected all data on demography (age and sex), clinical features of the FDE (shape, size, number, localization and number of episodes), and drug intake (dose, time between drug intake and symptom onset, and resolution after drug withdrawal).

Patch testing with piroxicam was performed at least 6 weeks after resolution of the preceding acute flare of FDE, and patch testing with meloxicam was performed 2 weeks later. We prepared the test with crushed tablets of piroxicam and meloxicam. Patch tests with the two drugs (10% pet.) were applied under occlusion for 48 hours in Finn Chambers, (SmartPractice, Canada) both lesionally, in hyperpigmented areas, and on healthy skin.⁷ Patch test readings were performed 2, 3 and 4 days later. We considered erythema or infiltration, associated or not with pruritus, as a criterion for positivity of the patch test.⁸

Patients with negative skin test results underwent an oral provocation test (OPT) with a 15-mg daily dose of meloxicam for 3 days. On the first day, the patient was given the full dose in three steps (5 mg in each step). On the second and the third days, the full dose was taken in one step. Follow-up of the patients was performed over the following week.

3 | RESULTS

Among 16 cases of NSAID-induced FDE recorded in our database, seven (46%) were considered to be related to piroxicam. There were two males and five females. The mean age of our patients was 40 years (range 26–55 years) (Table 1). All patients were diagnosed clinically. The lesions were between 1 and 5 cm in size, were well demarcated, and left residual hyperpigmentation. The FDE was multiple (two to four lesions) in five patients and solitary in two. Bullous eruptions were noted in two cases. The upper extremities were involved in five cases, followed by the face and the trunk, whereas the mucous membranes were not affected.

Six patients had multiple episodes (two to four) and one patient had only a single episode. The time between drug intake and cutaneous symptoms averaged 2 days (2 hours to 3 days). After withdrawal of piroxicam, the eruption had resolved, leaving residual

hyperpigmentation in all cases. Lesional patch tests for piroxicam were performed in six patients, and gave positive results in all of them on the day 2 reading. No positive reactions were observed in non-lesional test sites. For the remaining patient, an accidental rechallenge helped to establish the causality between piroxicam and the FDE. To assess cross-reactivity with meloxicam, patch tests were performed in all seven patients. Only one patient reacted positively (day 2 reading). The six remaining patients underwent an OPT with meloxicam, and only two had a relapse of their lesions, on day 2 and day 3, respectively (Table 1). No new lesions were observed after the OPT.

4 | DISCUSSION

In our case series, we present an assessment of cross-reactivity between piroxicam and meloxicam in FDE induced by piroxicam. As oxicams are chemically related,⁹ when an FDE induced by an oxicam agent occurs, it could be argued that it might also occur after a subsequent exposure to another oxicam agent, and that all oxicams should therefore be avoided. We have shown that this notion is not generally applicable, as 57% of our patients with piroxicam-induced FDE tolerated meloxicam.

On the basis of the Naranjo scale,⁶ piroxicam was the culprit drug in FDE, owing to a suggestive temporal relationship and a positive patch test result. The commonly implicated NSAIDs are phenylbutazone, ibuprofen, naproxen, and celecoxib.² Piroxicam, which is a widely used anti-inflammatory drug, has very rarely been associated with FDE. The first case was described in 1989 by Valseehee and Caimelli.¹⁰ Subsequently, a few case reports and a nine-case series of piroxicam-induced FDE were published in the medical literature.^{9–19} We consider that the clinical manifestations in the present series were consistent with previously published data.^{12–15,18}

It is well known that patch tests in residual lesions are highly recommended to identify the culprit agent in cases of FDE.²⁰ Andrade et al¹⁹ retrospectively evaluated the diagnostic value of patch testing in establishing an aetiological diagnosis in patients with FDE. Their 20-year experience indicated that patch tests allowed the identification of the offending drug in nearly half of patients (40.4%), particularly when NSAIDs were suspected. In our case series, the identification of the culprit drug (piroxicam) was enabled by patch testing in six of seven patients. This underscores the usefulness of this

TABLE 1 Demographic and clinical characteristics of the patients

Patient	Sex	Age (y)	Time interval (to last episode)	Number of plaques	Bullous eruption	Lesional patch test reaction to piroxicam	Cross-reactivity to meloxicam	
							Lesional patch test reaction to meloxicam	Oral provocation test reaction to meloxicam
1	M	55	2 d	4	+	+	–	–
2	M	44	2 d	2	–	+	–	+
3	F	48	2 h	2	–	+	–	–
4	F	39	3 d	1	+	ND	–	–
5	F	32	2 d	2	–	+	–	+
6	F	26	1 d	1	–	+	+	ND
7	F	40	3 h	3	–	+	–	–

Abbreviations: F, female; M, male; ND, not done.

Bullous eruption: +, present; –, not present. Patch test or oral provocation test: +, positive; –, negative.

test in the assessment of the causal relationship between piroxicam and FDE.

To examine cross-reactivity with meloxicam (the only oxycam available in Tunisia in addition to piroxicam) in patients with piroxicam-induced FDE, we performed patch tests and/or OPTs. Only three of seven patients showed cross-reactivity with meloxicam, and only one patient had a positive patch test reaction to meloxicam. In view of a lack of data on the patch test negative predictive value,² cross-reactivity with meloxicam was established by positive OPT results in the two remaining patients. We performed the OPT with meloxicam as described by Rahman et al.²¹ They have proposed giving one quarter to one half of the therapeutic dose on the first day, and then the full therapeutic dose on the second and third days, if there is still no reaction. positivity of the test was seen on day 2 and day 3 in our patients. Conversely, Sehgal et al.²² have suggested administering the drug at increasing doses up to a cumulative therapeutic dose in only 1 day.

In contrast to photosensitivity to piroxicam,²³ cross-reactivity with other oxycams in cases of piroxicam-induced FDE has been reported in sporadic case reports. For example, Gastaminza et al.¹³ described a patient with piroxicam-induced FDE who cross-reacted to tenoxicam. Similarly, Ordoqui et al.⁹ described two cases of piroxicam-induced FDE with cross-reactivity with both tenoxicam and droxycam confirmed by a positive patch test reaction in one patient and a positive OPT result in the other. Cross-reactivity with meloxicam in patients with piroxicam-induced FDE has been described in only one study.¹⁹ The authors reported that, in a series of 52 patients with drug-induced FDE, nine cases were induced by piroxicam. In those patients, patch tests with meloxicam gave positive results in only two patients, and OPTs with this drug were not performed.

In conclusion, we add to the medical literature seven cases of FDE induced by piroxicam, mostly confirmed by a positive patch test reaction, and we have shown potential cross-reactivity with meloxicam among these patients. Patch tests constitute a valuable and safe tool for the determination of the causal relationship between piroxicam and FDE. However, they seem to have poor predictive value for the assessment of cross-reactivity with meloxicam. For that, the OPT has to be used. However, more studies are required in order to define a reliable diagnostic procedure. Clinicians should be aware that meloxicam is not a safe alternative in patients with piroxicam-induced FDE, and that OPTs can be used to confirm tolerance before this drug is prescribed as a safe alternative.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ORCID

Haifa Ben Romdhane  <https://orcid.org/0000-0002-5755-5117>

Helmi Ammar  <https://orcid.org/0000-0002-9094-7243>

Amel Chaabane  <https://orcid.org/0000-0001-9703-1943>

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