

Allergic and photoallergic contact dermatitis from etofenamate: study of 14 cases

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Etofenamate is a non-steroidal anti-inflammatory drug (NSAID) commonly used for topical application in Mediterranean countries. Contact allergy to etofenamate has been rarely described. We report 14 cases of allergic and/or photoallergic contact dermatitis due to etofenamate.

Materials and Methods

We identified 14 cases of allergic and/or photoallergic contact dermatitis due to etofenamate seen by us during the last 8 years. The clinical data are summarized in Table 1. The most common sites of involvement of the reactions were feet, legs and neck, with onset being noted between 2 and 15D after the first topical application of the drug, except for Case 7 (30D). In some cases, bullous lesions were seen (Fig. 1a). All patients had a history of using with one or more NSAID topical products containing etofenamate. In Cases 2 and 13, previous use of Fastum[®] gel (containing ketoprofen) and Enangel[®] gel (containing dexketoprofen) respectively, were reported.

Table 1. Clinical data of patients investigated for contact allergy to etofenamate

Case number	Sex	Age	Onset time (D)	Location
1	Female	21	<10	Legs and hands
2	Female	58	7	Right arm and right neck
3	Male	29	7	Right foot
4	Female	58	<10	Both arms, shoulders and neck
5	Female	67	3	Neck
6	Female	48	2	Right elbow
7	Male	70	30	Hands
8	Male	30	2	Both feet and right forearm
9	Female	30	<10	Left foot and hand
10	Female	57	<10	Right knee and arm
11	Female	49	<10	Lower part of legs and feet
12	Female	17	<10	Right knee
13	Male	53	<4	Feet
14	Female	44	<15	Face, neck and right arm



Fig. 1. (a) Bullous lesions on right foot in Case 3. (b) Photopatch test at 1 D in Case 3.

All patients were patch tested to an NSAID series (Aristegui[®] Labs, Bilbao, Spain). Etofenamate (supplied by Chiesi[®] Labs) was tested at 1%, 5% and 10% in pet., as well as with the actual commercial medicament used by the individual patient when possible (Flogoprofen[®] gel and Aspitopic[®] gel), with 2D occlusion and readings according to the International Contact Dermatitis Research Group (ICDRG) criteria. Photopatch tests were performed in 10 patients with the NSAID series being applied in duplicate on either side of the upper back. After 1D, one series was uncovered and irradiated with 5 J/cm² UVA (Waldmann UV/PUVA 800; H. Waldmann GmbH & Co, Willingen-Schwenningen, Germany, calibrated with Waldmann UV-Meter) except for Case 9 (7.5 J/cm²). The first reading was performed 1 D after UVA exposure and the second 2 D later.

The results of patch and photopatch tests are summarized in Table 2. We found seven cases of allergic contact dermatitis (Cases 1, 6, 8, 9, 11, 12 and 14), five cases of photoallergic contact dermatitis (Cases 2, 3, 5, 7 and 13) (Fig. 1b) and two cases of combined allergic and photoallergic

contact dermatitis (Cases 4 and 10). In Case 4, previous use of a sun-tan cabin was reported by a patient (Fig. 2). In Case 2, a concomitant positive photopatch test to ketoprofen 1% in pet. was found. In Case 13, positive reactions were seen to ketoprofen, dexketoprofen and piketoprofen in the photopatch tests (probably due to cross-reaction between arylpropionic derivatives) with additional photoallergy to Enangel[®] (containing dexketoprofen). In most cases, studies with the constituents of the commercial medicaments were not performed. Twenty healthy controls were negative in both patch and photopatch tests with etofenamate. Active sensitization was not observed.

Discussion

Etofenamate, [2-(2-hydroxyethoxy)ethyl-*N*-($\alpha\alpha\alpha$ -trifluoro-*m*-tolyl)anthranilate], is an anthranilic acid derivative with analgesic, antirheumatic, antipyretic and anti-inflammatory properties. It is a non-selective COX inhibitor affecting also the lipo-oxygenase pathway. It is used as a cream or gel for topical application. The commercial forms marketed in Spain are Flogoprofen[®],

Table 2. Results of patch and photopatch tests to etofenamate

Case number	Allergens	PT		PPT	
		D2	D4	D1	D3
1	Flogoprofen [®] gel as is	++	++	NT	NT
	Etofenamate 1% pet.	–	–	NT	NT
	Etofenamate 5% pet.	–	–	NT	NT
	Etofenamate 10% pet.	–	++	NT	NT
2	Flogoprofen [®] gel as is	NT	NT	NT	NT
	Etofenamate 1% pet.	–	–	+++	+++
	Etofenamate 5% pet.	–	–	+++	+++
	Etofenamate 10% pet.	–	–	+++	+++
	Ketoprofen 1% pet.	–	–	+++	+++
3	Flogoprofen [®] gel as is	NT	NT	NT	NT
	Etofenamate 1% pet.	–	–	+++	+++
	Etofenamate 5% pet.	–	–	+++	+++
	Etofenamate 10% pet.	–	–	+++	+++
4	Flogoprofen [®] gel as is	NT	NT	NT	NT
	Etofenamate 1% pet.	++	++	+++	+++
	Etofenamate 5% pet.	++	++	+++	+++
	Etofenamate 10% pet.	++	++	+++	+++
5	Aspitopic [®] gel as is	–	–	+	++
	Etofenamate 1% pet.	–	–	–	+
	Etofenamate 5% pet.	–	–	–	+
	Etofenamate 10% pet.	–	–	–	+
6	Flogoprofen [®] gel as is	NT	NT	NT	NT
	Etofenamate 1% pet.	+++	+++	+++	+++
	Etofenamate 5% pet.	+++	+++	+++	+++
	Etofenamate 10% pet.	+++	+++	+++	+++
7	Aspitopic [®] gel as is	NT	NT	NT	NT
	Etofenamate 1% pet.	–	–	–	+
	Etofenamate 5% pet.	–	–	+	++
	Etofenamate 10% pet.	–	–	++	++
8	Flogoprofen [®] gel as is	+++	+++	NT	NT
	Aspitopic [®] gel as is	+++	+++	NT	NT
	Etofenamate 1% pet.	+++	+++	NT	NT
	Etofenamate 5% pet.	+++	+++	NT	NT
	Etofenamate 10% pet.	+++	+++	NT	NT
9	Aspitopic [®] gel as is	+++	+++	–	–
	Doctofril [®] as is	–	–	–	–
	Etofenamate 1% pet.	++	++	–	–
	Etofenamate 5% pet.	+++	+++	–	–
10	Etofenamate 10% pet.	+++	+++	–	–
	Aspitopic [®] gel as is	NT	NT	NT	NT
	Reflex [®] spray as is	–	–	–	–
	Etofenamate 1% pet.	–	+	+	++
	Etofenamate 5% pet.	–	+	+	++
11	Etofenamate 10% pet.	–	+	+	++
	Flogoprofen [®] gel as is	NT	NT	NT	NT
	Etofenamate 5% pet.	+	++	–	++
	Aspitopic [®] gel as is	+++	+++	NT	NT
12	Etofenamate 1% pet.	+	+	NT	NT
	Etofenamate 5% pet.	+++	+++	NT	NT
	Etofenamate 10% pet.	+++	+++	NT	NT
	Flogoprofen [®] gel as is	–	–	++	++
13	Reflex [®] spray as is	–	–	–	–
	Ketoprofen 1% pet.	–	–	++	++
	Piketoprofen 1% pet.	–	–	+	++
	Piketoprofen 2% pet.	–	–	++	++
	Dexketoprofen 1% pet.	–	–	+++	+++
	Dexketoprofen 2% pet.	–	–	+++	+++
	Etofenamate 1% pet.	–	–	+	++
	Etofenamate 5% pet.	–	–	++	++
	Etofenamate 10% pet.	–	–	++	++
	Aspitopic [®] gel as is	++	++	NT	NT
14	Etofenamate 1% pet.	+	+	NT	NT
	Etofenamate 5% pet.	++	++	NT	NT
	Etofenamate 10% pet.	++	++	NT	NT
	Aspitopic [®] gel as is	++	++	NT	NT

NT, not tested; –, negative; +, ++, +++, scores using ICDRG criteria

Aspitopic[®] and Zenavan[®]. Local side effects are usually described as pruritus and local erythema.

At present, approximately 20 cases of allergic or photoallergic contact dermatitis from etofenamate have been described in the English literature (1–11). Other cutaneous reactions such as urticaria or angioedema (12) and exfoliative dermatitis (13) have also been described.

The interpretation of reactions in our patients was as follows: (i) negative (negative in both irradiated and unirradiated sets); (ii) irritant reactions (occurring in one or both sets, showing a decrescendo pattern); (iii) photoallergic reaction (delayed crescendo pattern in the irradiated set only); (iv) allergic contact reaction (delayed crescendo pattern to the allergen in both irradiated and unirradiated sets, or in the unirradiated set alone); (v) combined allergic and photoallergic contact reaction (contact reaction but at least one ICDRG grade stronger in the irradiated set), although it must always be interpreted with caution as there are authors who believe they can be cases of photo aggravated allergic contact dermatitis. In our series, seven cases were diagnosed as pure allergic contact dermatitis, five cases as photoallergic contact dermatitis and two cases as a probable combined allergic and photoallergic contact dermatitis based on clinical grounds and investigations. The latter two cases (Cases 4 and 10) are similar to those previously described by Sánchez Pérez et al. (14).

We could not perform patch tests with other anthranilic acid derivatives (meclofenamate, niflumic acid and mefenamic acid) to study any possible cross-reactivity. Two reports of cross-reaction between etofenamate and flufenamic acid (one case of allergic contact dermatitis and other case of photoallergic contact dermatitis) have been published, probably based on their similar chemical structure (flufenamic acid is an etofenamate ester) (7, 9). There are no case reports of cross-reactivity among different groups of NSAIDs (11, 15), but we found two cases with a concomitant photoallergy (not a true cross-reaction) from aryl-propionic derivatives (ketoprofen and dexketoprofen).

We report the largest published series of cutaneous allergic reactions to etofenamate. In our experience, etofenamate is now the second most frequent NSAID causative agent of contact and photocontact dermatitis after



Fig. 2. Eczematous reaction on the left shoulder after UVA exposition in Case 4.

arylpropionic derivatives (dexketoprofen and ketoprofen) (16). We consider that these NSAIDs ought to be included in routine photopatch tests series.

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