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Multiple Cutaneous Sensitization to Nonsteroidal Anti-Inflammatory Drugs

Key Words

Allergic contact dermatitis
Cross-reactions
Nonsteroidal anti-inflammatory drugs
Patch tests

Abstract

The use of topical nonsteroidal anti-inflammatory drugs is widespread (particularly in countries bordering the Mediterranean). Compared to their wide use, the incidence of published adverse cutaneous effects appears minimal, although they are increasing. Most of them are a form of allergic contact dermatitis (ACD). Multiple sensitization and/or cross-reactions are rarely reported. Interestingly, our patient presented ACD with diclofenac and etofenamate (both from different chemical groups) and, furthermore, patch tests were positive with bencydamine and indomethacin (both indolacetic acid derivatives), piroxicam and fepradinol. We think that our results could not be explained due to cross-reactivity, and that multiple sensitization was more likely.

Since their introduction in the 1970s, the use of topical nonsteroidal anti-inflammatory drugs (NSAIDs) has become widespread (particularly in countries bordering the Mediterranean). Compared to their wide use, the incidence of published adverse cutaneous effects appears minimal, although they are increasing. Most of them are a form of allergic contact dermatitis (ACD), but some, particularly those induced by propionic acid derivatives, are identified as photoallergic contact dermatitis [1]. Multiple sensitization and/or cross-reactions are rarely reported [2].

Case Report

A 40-year-old man, with no atopic or allergic contact dermatitis history, was treated for an acute inflammation on his right elbow with Voltaren Emulgel® (diclofenac) twice daily. Ten days later he developed an itchy and vesicular eruption in this area, which disappeared within 1 week after discontinuing treatment. A similar reaction occurred on his left wrist when 4 months later he applied Flogoprofen® (etofenamate) spray twice daily. Previously, he had used topical NSAIDs (he could not remember which) on several occasions without problems.

Epicutaneous tests were carried out with the ICDRG standard series (Martí Tor S.A., Barcelona, Spain), with Voltaren Emulgel and Flogoprofen spray and their components (table 1), and with a battery of NSAIDs (table 2). Drugs used in test preparations were obtained from the trade name dealers in Spain. Patch tests were performed on the back (normal skin) using Leukotest® (Beiersdorf AG, Hamburg, Germany) covered by Mefix® (Mölnlycke Health Care AB, Sweden). The

patch test readings were conducted according to ICDRG guidelines at 48, 72 and 96 h. Voltaren Emulgel and Flogoprofen spray were positive. The GEIDC standard series and the Voltaren and Flogoprofen components (excepting the active drug) proved negative. The results of the NSAID battery are shown in table 2.

NSAIDs were selected among those marketed in Spain. Vehicles and concentrations were established by considering previous ex-

Table 1. Qualitative composition

Voltaren Emulgel ¹	Flogoprofen spray ²
Diclofenac	Etofenamate
Caprylic acid	Propylene glycol
Desionized water	Menthol
Polyethylene glycol	Ethyl alcohol
Diethylamine	Turpentine essence
Propylene glycol	
Liquid petrolatum	
Cinnamon essence	
Carbomer	

¹ Provided by Geigy Laboratory, Barcelona, Spain.

² Provided by Wassermann Laboratory, Barcelona, Spain.

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1018-8665/96/1931-0059\$10.00/0

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Received:
August 14, 1995
Accepted:
January 19, 1996

Table 2. NSAID series

Drug	Chemical group	Vehicle	Results after		
			48 h	72 h	96 h
Niflumic acid	Anthranilic acid derivative	3% pet	—	—	—
Etofenamate	Anthranilic acid derivative	5% pet	—	++	++
Benzydamine	Indolacetic acid derivative	5% pet	—	+++	+++
Indomethacin	Indolacetic acid derivative	5% pet	+++	+++	+++
Diclofenac	Arylacetic derivative	1% pet	—	+++	+++
Piroxicam	Oxicam derivative	0.5% pet	—	++	++
Fepradinol	Adrenergic compound	6% pet	++	+++	+++
Isonixin	Nicotinic acid derivative	2.5% pet	—	—	—
Ketoprofen	Arylpropionic derivative	1% pet	—	—	—
Naproxen	Arylpropionic derivative	10% pet	—	—	—
Pyrazinebutazone	Pyrazolone derivative	5% pet	—	—	—
Salicylate diethylamine	Salicylate	10% pet	—	—	—

periences published by other authors [1], and when these were not available, a concentration in pet similar to the commercial preparation was used. The same battery was tested on 20 controls with negative results.

Discussion

Representative NSAIDs show considerable structural heterogeneity [1]. Cross-sensitivity and photo-cross-sensitivity are described among the NSAIDs in the same group (e.g., among the pyrazolones and propionic acid derivatives) [2–7]. There are no case reports of cross-reactions among different groups [1, 2]. Interestingly, our patient presented ACD with diclofenac and etofenamate (both from different groups) and, further-

more, patch tests were positive with benzydamine and indomethacin (both indolacetic acid derivatives), piroxicam and fepradinol. Although etofenamate and niflumic acid are included in the same group (anthranilic acid derivatives), the first was positive and the second negative. Fepradinol represents a special case because, structurally, it belongs to the group of adrenergic compounds [8]; moreover, no cross-reactivity with other NSAIDs has been observed in previous references [9, 10].

We searched for structural analogies among the different NSAIDs to detect a particular chemical component, but we did not find any. However, we found that drugs with positive results share a high degree of 'nucleophilia' (tendency to give electrons); on the contrary, drugs with negative results are

'electrophilic' (tendency to take electrons). The first could react with other compounds more easily than the second [11].

Finally, we think that our results cannot be explained by cross-reactivity, and that multiple sensitization is more likely. Perhaps, the frequent use of topical NSAIDs facilitated the sensitization.

Acknowledgement

We thank Ana Mata Durán (Professor of Biochemistry, University of Extremadura, Spain) and Alonso Montero Murillo (Assistant Professor) for their helpful review of the manuscript.

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