

Greater allergenicity of topical ketoprofen in contact dermatitis confirmed by use

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The use of topical non-steroidal anti-inflammatory drugs (NSAIDs) is very popular in spite of their doubtful efficacy and high number of generally not serious, but preventable, adverse effects, especially photoallergy. The allergenic potential of different topical NSAIDs was determined by performing a retrospective observational study of the period 1996–2001 and comparing the cases of allergy and photoallergy with the use of each topical NSAID. The diagnoses were obtained from a review of the clinical records of patch/photopatch testing carried out in the dermatology departments of 2 public hospitals in Bizkaia (Spain). The use of the different topical NSAIDs was obtained from invoices sent to the National Health System and the Reporting odds ratio (ROR) and Proportional reporting ratio (PRR) disproportionality estimates of the FEDRA database of the Spanish Pharmacovigilance System. A total of 139 contact reactions to topical NSAIDs were found with ketoprofen being responsible for 28% of the allergies and 82% of the contact photoallergies in spite of not being the most used topical NSAID (third in the ranking, diclofenac was the first). The ROR for ketoprofen was 3.9 (2.4–6.4) and the PRR 3.4 (2.1–5.5), thus confirming the possibility of a warning signal. The results support the need for regulatory action on topical ketoprofen.

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Little evidence is available on the efficacy of the administration of non-steroidal anti-inflammatory drugs (NSAIDs) by topical route, even though they are widely used in the treatment of many rheumatic disorders (1–6). Some topical NSAIDs (ketoprofen, diclofenac, ibuprofen and piroxicam among others) are available in a large number of countries, often without a medical prescription (piketoprofen and ibuprofen).

There are many references published on the adverse effects of NSAIDs after administration by topical route even though, in general, they are individual cases or in reference to a particular NSAID (7–12). Furthermore, over the years, the number of medicinal products used by this route has increased and, as a result, there is also an increase in the number of adverse reactions which, even though they mainly appear on the skin, may cause more generalized reactions (13–16). Some countries, such as France, have modified the conditions of use for some of them, ketoprofen in particular (17), because of

the notification of a large number of photosensitivity reactions (18).

Therefore, as photosensitivity reactions are the most notorious for topical NSAIDs, it would seem important to determine the number of cases of allergy and photoallergy, as well as their consumption, in order to verify the hypothesis that the number of cases is not directly related to use but that there are certain topical NSAIDs that are more allergenic. Considering that the diagnosis of allergy and photoallergy is usually made in the dermatology departments of hospitals, it was considered appropriate to make the study at this healthcare level, together with an analysis of their use in the healthcare area of these departments.

On the other hand, since 1982, the Spanish Pharmacovigilance System (SEFV) has collected and filed in its database all reports of suspected adverse reactions and this, in the case of topical NSAIDs and the contact allergy reactions, enables comparing the reporting rates and use

another route to verify the hypothesis that some topical NSAIDs are more allergenic.

Materials and Methods

The data collected in the interval 1996–2001 inclusive were studied using a retrospective observational method based on the diagnosis of allergy and/or photoallergy after a patch and photopatch test in the Dermatology Departments of Hospital de Cruces and Hospital de Galdakao, whose coverage is 73% (828 239 inhabitants) of the population of the territory of Biskay in Spain. The data were only taken from clinical records with positive results for contact allergy and photoallergy to topical NSAIDs. The information included the age, sex and profession of the patient, location of the lesion, suspect medication, personal and family background of allergy and the result of the patch and/or photopatch test.

Diagnosis in the Dermatology Departments uses the European standard series 'True Test' (19) as well as testing with allergens of specific batteries, in this case anti-inflammatory drugs and other allergens according to the patient's clinical record. The photopatch tests were carried out according to the method described by the Spanish photobiology group (20). All patients underwent patch testing by applying a standard and specific series according to the clinical record to the upper part of the back and covering it with a hypoallergenic adhesive plaster. A first reading was made at 48 hr and another at 96 hr (21). The patients with clinical suspicion of photoallergy were also submitted to the photopatch test, which involved the application of 2 series of allergens. 1 of the series was irradiated at 48 hr with a Waldmann 7001/k lamp (10J/cm²; Tecnosa SA, Espluges de Llobregat, Spain), and a reading was made of both series (irradiated and not irradiated) at 96 hr.

Furthermore, the Pharmacovigilance Unit of the Basque Country (network of centres of the Spanish Pharmacovigilance System, SEFV) provided reporting data from the whole SEFV to estimate the Reporting odds ratio (ROR) and the relationship between the Proportional reporting ratio (PRR), both indicators used by pharmacovigilance systems for the detection of warning signs (the UK considers this to be a $PRR \geq 2$, $\chi^2 \geq 4$ and the number of reports with the association ≥ 3 (22); Holland considers it a warning sign when the lower limit of the 95% confidence interval of the ROR is higher than 1) (23).

The use of each topical NSAID was obtained from data on the invoices sent to the National Health System (NHS), the Ministry of Health

and Consumer Affairs and the RAEFAR database (Register and Authorization of Pharmaceuticals) based on the units sold as this medication group does not have a DDD (defined daily doses) assigned by the ATC/DDD system because of the difficulty of establishing the daily maintenance dose for the form of application of this medication.

Results

There were 139 cases of contact reactions to topical NSAIDs, 56 (40.3%) allergies and 83 (59.7%) photoallergies, corresponding to 101 patients with a mean age of 48 years (range 14–99 years), 95 reactions (68.3%) were in women and 44 (31.7%) in men. By age, there were 2 cases (1.4%) in the interval of 0–14 years, 31 cases (22.3%) in the interval of 15–30 years, 30 cases (21.6%) in the interval of 31–45 years, 33 cases (23.7%) in the interval of 46–60 years, 29 cases (20.8%) in the interval of 61–75 years and 11 cases (7.9%) in the interval of 76–99 years; in 3 cases (2.1%), the age was unknown.

The topical NSAID which showed the most cases of allergy was ketoprofen, 16 (28.6%). In the second place was piroxicam with 12 allergies, of which 4 simultaneously presented contact allergy to other NSAIDs (ketoprofen, naproxen, diclofenac, etofenamate and salicylates). In the third place was etofenamate with 10 cases. This was followed by salicylate with 4 cases and diclofenac and fepradinol with 3 cases each. It is interesting to note the existence of a single case of allergy to piketoprofen, a patient who also presented photoallergy to ketoprofen.

Ketoprofen was also outstanding in regard to photoallergies with 68 cases (81.9%). The other NSAIDs are far behind, with only 15 cases, 9 for piroxicam, 4 for piketoprofen and 1 each for phenylbutazone and benzydamine. Of the 9 cases of photoallergy to piroxicam, 7 presented allergy to thimerosal, one allergy to ketoprofen and one that was not tested. In the case of piketoprofen, 3 patients presented cross-reaction to ketoprofen (1 also to the mixture of fragrances) and the fourth patient presented allergy to the mixture of fragrances.

The complete distribution of the cases of allergy and photoallergy by year (1996–2001) is described in Table 1, together with indications of the accumulated incidence (AI) per million inhabitants for each active principle.

The data on the use of the different topical NSAIDs during the period 1996–2001 show diclofenac in the first position as the NSAID most sold (554 332 units), far above piketoprofen

Table 1. Cases of allergy and photoallergy to topical NSAIDs in the study, 1996–2001

Generic name	Allergy							Photoallergy							Total	AI $\times 10^6$
	96	97	98	99	00	01	Subtotal	96	97	98	99	00	01	Subtotal		
Ketoprofen	4	1	3	5	0	3	16	10	9	13	21	5	10	68	84	101.4
Piroxicam	1	0	2	2	2	5	12	0	0	2	3	2	2	9	21	25.3
Etofenamate	0	3	0	2	1	4	10	0	0	0	0	0	0	0	10	12.1
Piketoprofen	0	0	0	1	0	0	1	0	1	0	0	1	2	4	5	6.0
Salicylates	0	0	0	2	0	2	4	0	0	0	0	0	0	0	4	4.8
Fepradinol	0	1	1	0	0	1	3	0	0	0	0	0	0	0	3	3.6
Diclofenac	1	1	0	0	0	1	3	0	0	0	0	0	0	0	3	3.6
Indomethacin	1	1	0	0	0	0	2	0	0	0	0	0	0	0	2	2.4
Phenylbutazone	0	1	0	0	0	0	1	1	0	0	0	0	0	1	2	2.4
Benzydamine	0	0	0	0	0	1	1	0	1	0	0	0	0	1	2	2.4
Aceclofenac	0	0	1	0	0	0	1	0	0	0	0	0	0	0	1	1.2
Naproxen	0	0	0	0	0	1	1	0	0	0	0	0	0	0	1	1.2
Mabuprofen	0	1	0	0	0	0	1	0	0	0	0	0	0	0	1	1.2
	7	9	7	12	3	18	56	11	11	15	24	8	14	83	139	

AI, accumulated incidence.

(346 563), ketoprofen (310 095), piroxicam (156 977), etofenamate (146 298), aceclofenac (112 142) and the others. As can be seen in Fig. 1 which simultaneously shows the use of each NSAID and the number of cases of allergy and photoallergy, for the majority of topical NSAIDs (piroxicam, etofenamate, fepradinol, indomethacin, aceclofenac, benzydamine and naproxen), there is agreement between use and the number of cases of allergy. However, for some NSAIDs that are extensively used (diclofenac and piketoprofen), the number of cases is very small. On the other hand, there is a disproportion for ketoprofen, which represents a

majority of cases, although its use is half that of diclofenac and even less than piketoprofen.

The ROR of ketoprofen for photosensitivity reactions compared to other NSAIDs by topical route and other adverse reactions (not photosensitivity), in the FEDRA database of the Spanish Pharmacovigilance System, was 3.9 (95% CI = 2.4–6.4). In the same way, the relationship between the PRR for ketoprofen and photosensitivity reactions compared to other NSAIDs by topical route and the other adverse reactions (not photosensitivity) was 3.4 (95% CI = 2.1–5.5) (Table 2); both indicators are above the minimum limit considered as a warning signal.

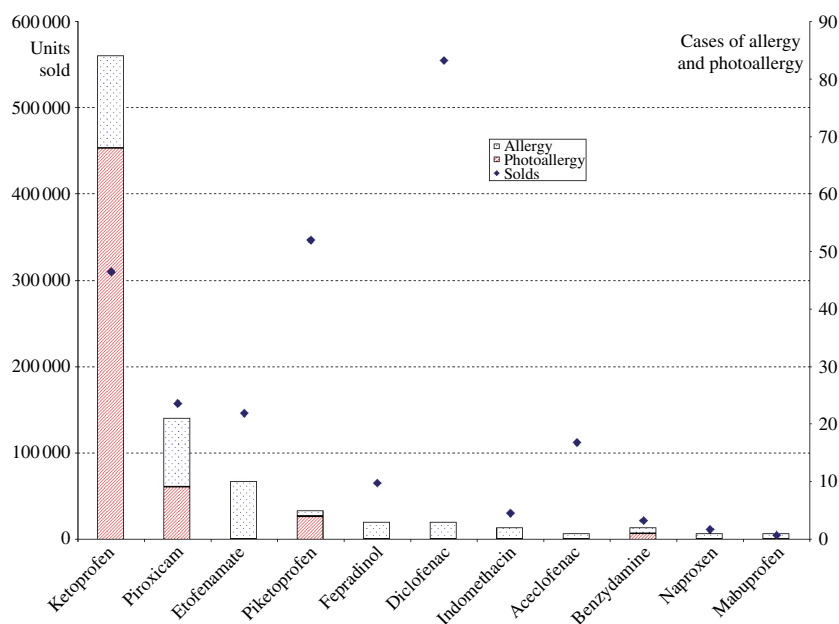


Fig. 1. Cases numbers of allergy and photoallergy to each topical NSAID (in bars, on the right). In rhombus, on the left, units sold of each NSAID (1996–2001).

Table 2. Reporting odds ratio (ROR) and proportional reporting ratio (PRR) of photosensitivity associated with ketoprofen versus the rest of topical NSAIDs in the Spanish Pharmacovigilance database

	Photosensitivity	Rest of ADR	Total reports
Topical ketoprofen	53	218	271
Rest of topical NSAIDs	27	436	463
Total reports	80	654	734

ROR = 3.9 (95% CI 2.4–6.4); PRR = 3.4 (95% CI 2.1–5.5); $\chi^2 = 33.16$.

Discussion

In this study, ketoprofen is the topical NSAID that has caused most contact allergies/photoallergies, and this coincides with other authors (24, 25). However, the data on sales by active principle indicate that ketoprofen is not the most sold, it is used 79% less than diclofenac and 12% less than piketoprofen, medications responsible for only 2.1% and 3.6% of the contact reactions in the study.

Among the explanations for this disagreement between use of ketoprofen and the number of cases of photoallergies, it is important to note that on the one part, photochemical and photobiological studies of topical NSAIDs show that derivatives of 2-arylpropionic acid (naproxen, ibuprofen, ketoprofen and suprofen) were the most photoactive (26); the action of UV light mainly transforms ketoprofen into CO₂ and 3-ethyl-benzophenone, the molecule responsible for the photoallergy (27–30). On the other hand, for piketoprofen, in spite of also being an NSAID of the arylpropionic group, with a structure derived from benzophenone, only 5 cases were found in the study (4 with cross-reaction to ketoprofen), even though it was more often sold than ketoprofen. One explanation of this low number of photoallergies to piketoprofen could be that just like other active principles of the arylpropionic group (like ibuprofen), its absorption spectrum is very weak with the consequent difficulty of forming a photoactive derivative (3-ethyl-benzophenone) (26), although, should this form, it would be equally photoactive, irrespective of the original arylpropionic drug. This could explain the cases of photoallergy and cross-reactions for both ketoprofen and piketoprofen.

The results of photoallergy to piroxicam with allergy to thimerosal (7 cases out of 9), found in the study, coincide with Vasconcelos et al. (31), who refer to 10 cases of allergy to thimerosal in 11 patients with photoallergy to piroxicam, even though it was administered by oral route. These reactions are probably due to exposure to

ultraviolet A light, resulting in a photoproduct with cross-reaction to thiosalicylic acid. The 4 cases of allergy where there was simultaneous allergy to ketoprofen, naproxen and etofenamate are probably due to co-sensitization, as the structure of each of these NSAIDs is not related to that of oxycam.

Diclofenac only caused 3 allergies and no photoallergy, in spite of being the most sold topical NSAID. This fact, together with the shortage of published cases (32), could be explained by the biochemical theory presented by Moore (26), who described how diclofenac, through the action of ultraviolet radiation, loses the chlorine substituents and closes its ring, producing carbazol-1-acetic acid, a weak phototoxic agent, which forms free radicals of short duration that have difficulty in reaching biological substrates to produce the photosensitivity reaction.

This study presents some limitations; on the one part, even though the diagnosis of allergy/photoallergy is made by specialists, according to the recommendations of the International Contact Dermatitis Research Group (ICDRG), the possibility of some cases of doubtful diagnosis cannot be excluded because of the subjective component involved in reading the patch/photo-patch test. Another limitation is that the usage data only refer to prescription medication financed by the NHS, even though some of these products can be obtained without a medical prescription or with a prescription not financed by the NHS. Furthermore, it does not include all cases existing within the geographical area of the study; in some cases, no confirmatory diagnostic tests are carried out because the clinical suspicion is very strong, and there is also the possibility of patients attending private clinics and finally, because the study could only cover the healthcare services of 73% of the population in the territory. Nevertheless, these limitations do not seem to substantially affect the representation of each topical NSAID in the observed results, neither for use nor for the number of cases, and do not affect the conclusion of greater allergenicity of ketoprofen in the group of topical NSAIDs.

The results support the need for regulatory action on topical ketoprofen.

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