

## ORIGINAL ARTICLE

# A pilot study on the incidence of severe photosensitivity reactions leading to hospitalization linked to topical ketoprofen and other medications in selected European regions

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## Keywords

Incidence study, NSAIDs, severe photosensitivity reactions, topical ketoprofen

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## Funding Information

The study was supported by an unrestricted research grant obtained from the Ketoprofen Consortium, which consists of Menarini Industrie Farmaceutiche Riunite S.r.l, Bayer S.p.A, Cyathus Exquirere Pharmaforschungs GmbH, Dompe' S.p.A, EG S.p.A, JSC Grindeks, Hisamitsu UK Ltd., Istituto Biochimico Italiano G. Lorenzini S.p.A, Italfarmaco S.p.A, Pierre Fabre Ibérica S.A, Sandoz International GmbH, Sanofi-Aventis Groupe.

Received: 18 December 2015; Revised: 11 January 2016; Accepted: 2 February 2016

*Pharma Res Per*, 4(3), 2016, e00225,  
doi: 10.1002/prp2.225

doi: 10.1002/prp2.225

## Abstract

The aim of this study was to assess the prevalence of exposure to topical nonsteroidal anti-inflammatory drugs (NSAIDs), particularly ketoprofen, in a convenience sample of the population, to obtain estimates of the incidence of severe photosensitivity leading to hospitalization, and to assess causative factors in three catchment areas: the Paris metropolitan area, the Lombardy region (Italy) and the Prague area. All cases of severe photosensitivity not explained by underlying conditions and admitted to hospitals in the selected areas were included in the study. Controls were patients consecutively admitted to hospitals, in the same areas, for an acute condition or for an elective procedure not suspected of being related to medication use. From October 2012 to September 2013, 920 controls were recruited (median age 44 years, 50.8% females); 8 severe photosensitivity cases were reported in the population aged 18–74 years of the 3 geographical areas during the 1-year surveillance period, corresponding to an incidence rate of 4.81 cases per 10 million person-years (95% confidence interval – CI, 2.07–9.48). Six controls reported 1-month exposure to topical ketoprofen, with an estimated prevalence of 0.65% (95% CI, 0.24–1.42). The population attributable risk for severe photosensitivity reactions linked to ketoprofen was 11.92% (95% CI, –0.12–52.99). This study was conducted in selected European areas and showed that the incidence of severe photosensitivity reactions leading to hospitalization as well as the exposure rate to topical ketoprofen were low. Among topical NSAIDs, topical ketoprofen was the leading cause of photosensitivity reactions but accounted for a limited number of hospitalized cases. Probably most of the relevant reactions were managed in the outpatient setting and a community based case–control study is advisable.

### Abbreviations

BMI, body mass index; ICC, intraclass correlation coefficient; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PACD, photoallergic contact dermatitis; PAR, population attributable risk.

## Introduction

Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic, and antipyretic properties. It is available in several forms including oral, parenteral, and topical preparations. The topical form of ketoprofen usually consists of a 2.5% to 5% gel, but there are other formulations (e.g., cream, liquid spray) and other strengths available. Topical ketoprofen is used to treat pain and inflammation in conditions such as minor trauma (sprains, bruising), tendonitis, small-joint osteoarthritis, acute low-back pain, and phlebitis. Topical ketoprofen is used in more than 70 countries worldwide. Since its first market authorization in Europe in 1972, cases of photoallergic contact dermatitis related to ketoprofen use have been described and characterized (Bagheri *et al.* 2000; Matthieu *et al.* 2004; Cantisani *et al.* 2010; Noize *et al.* 2010). To date, however, there is limited information on the incidence of severe photosensitivity reactions leading to hospitalization among topical ketoprofen users as compared with users of other topical NSAIDs. From spontaneous surveillance data, in France, originated in different areas and different time periods, it was estimated that the frequency of reporting of any cutaneous adverse events attributed to topical ketoprofen ranged from 0.8 to 2.8 per 100,000 inhabitants per year and that around 6–18% of these cutaneous side-effects were cases of photoallergy leading to hospitalization (Baudot *et al.* 1998; Veyrac *et al.* 2002; Noize *et al.* 2010). In an analysis of spontaneous reports in Italy, the observed reporting rate of photosensitivity reactions from any causes was 5.5 per 100,000 inhabitants per year and the rate of serious photosensitivity reactions was 0.09 per 100,000 inhabitants per year (Naldi *et al.* 1999). In another study conducted in Spain using clinical records of subjects with contact allergy and/or photoallergy due to topical NSAIDs, the rate of photoallergic reactions was 1.2 per 100,000 per year (Diaz *et al.* 2006). In order to better define the risk profile of topical ketoprofen use, as requested by the European Medicines Agency (EMA) in 2010, an epidemiologic case–control study was proposed focusing on severe photosensitivity reactions leading to hospitalization and assessing risks linked with the use of topical ketoprofen and other topical NSAIDs for these reactions. This paper reports the results of the pilot feasibility phase of this study. The aims of the pilot phase were first to assess the prevalence of exposure to topical

NSAIDs and specifically topical ketoprofen in a convenience sample of the population; second to develop diagnostic criteria for severe photosensitivity with special focus on photoallergic contact dermatitis (PACD), already reported elsewhere (Cazzaniga *et al.* 2015), and third to obtain estimates of the incidence of severe photosensitivity leading to hospitalization in selected sampling areas.

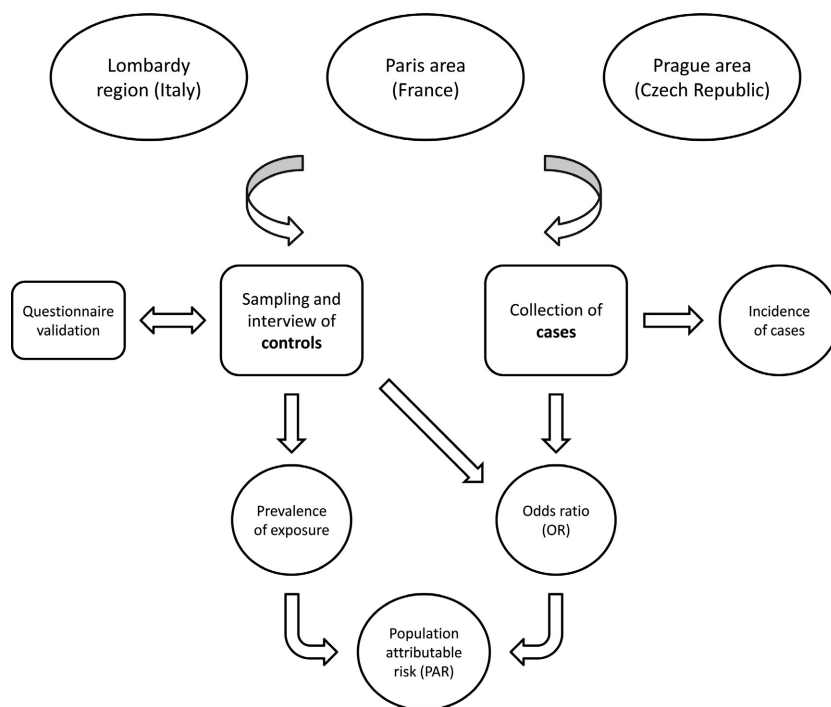
## Materials and Methods

The study was implemented as an incidence study linking incidence data with population drug exposure estimates derived from interviewing hospital controls deemed to be representative of the general population. Three geographical areas were surveyed: the Paris metropolitan area in France, the Lombardy region in Italy, and the Prague area in the Czech Republic. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards, and was approved by the ethical committees in each of the selected catchment areas: Ethics Committee of the province of Bergamo (resolution n. 997/2012); Institutional Review Board for the Protection of Human Subjects of Henri Mondor Hospital, Paris (resolution n. 2012/38NICB); Ethics Committee of Bulovka Hospital, Prague (resolution n. 7.8.2012/488/EK-Z). The general scheme of the study is shown in Figure 1.

### Collection of cases

This component of the study involved the identification, during the 1-year surveillance period, of all cases of severe photosensitivity from any cause admitted to hospitals in the surveyed areas (including Emergency Department admissions and 1-day admissions). The diagnostic criteria employed were in agreement with those developed during the first phase of our study (Cazzaniga *et al.* 2015). Seven criteria were identified by experts as relevant for the diagnosis of PACD. The criteria were related to the type of skin lesions, accompanying symptoms, skin area involved, general medical history, modality of exposure to the culprit substance, history of exposure to the sun or other light sources and photopatch test results.

All patients, aged between 18 and 74 years, admitted for a skin reaction associated with vesicles and/or bullae, involving one or several body areas, with a positive



**Figure 1.** Flow chart of the study, representing data collection in selected catchment areas and outcomes of interest.

history of sun exposure in the last month or week before hospitalization, and with a clinical diagnosis of photosensitivity reaction were included in the study. Patients with reactions attributable to the underlying diseases (e.g., systemic lupus erythematosus) and immunologically mediated photodermatoses (e.g., polymorphic light eruption) were excluded from the analysis. Patient's information was retrieved from hospital records and direct patient interview. Informed consent had been obtained from the patient in the latter case. Data on general demographics, suspected culprit substance, administration route, formulation, severity, and clinical outcome were collected. Drug exposure was defined as the use of drugs or medications within 1 month prior to the index date, i.e., the date of hospitalization. Drug exposure was assessed using a structured day by day questionnaire for the week preceding the index date and week by week for the preceding 3 weeks.

In addition to hospital surveillance, in the Lombardy region, cases were collected through two major study databases: MEREAFaPS and FARMAMONITO (Galfrascoli et al. 2012). The REACT network was also alerted for the reporting of photosensitivity cases and cross-checked with other registries for consistency and completeness (Gamba et al. 2014). For the Prague area, Directors of Dermatology Departments in every hospital of the area had been asked to report retrospective as well as

prospective cases to the local Coordinating Centre. For the Paris area, all cases were retrieved through the French Pharmacovigilance Database and direct surveillance of hospitals in the area (Durrieu et al. 2013).

### Control data

This part of the study involved the identification and interview of a sample of patients of both genders, aged between 18 and 74 years, consecutively admitted to hospitals in the geographic areas participating in the pilot phase and satisfying entry criteria for controls usually adopted in pharmacoepidemiologic case-control studies (Slone et al. 1977), namely, patients admitted for an acute condition or for an elective procedure not suspected of being related to medication use. Conditions included: traumatic injuries, acute infections, abdominal emergencies, elective surgery such as hernia repair, ocular, nose, and throat procedures. Patients with chronic disorders were eligible if hospitalized for an unrelated acute disease but not if admitted for an acute exacerbation of their chronic disease. Patients admitted for any skin problem suspected to be related to photosensitivity were excluded. The eligible controls were contacted and once informed consent had been obtained were interviewed according to a standardized questionnaire exploring medication use as well as other items such as demographics, recent and past

medical history (including reactions to topical NSAIDs), history of sun exposure during the last week and month preceding hospitalization, phenotypic features, and environmental exposure. Drug exposure for controls was defined in the same way as for cases.

A proportionate stratified sampling design without replacement was used in order to obtain a representative sample of the population within each geographical area (Kalton 1983). In the sampling plan, the distribution of the population by age, gender, and geographic location was accounted for. In each participating hospital, staff nurses and physicians were trained regarding proper data collection and coding system used for the interview before the beginning of the study. Interviews were performed within 10 days from hospital admission so as to ensure a proper recall of events prior to hospitalization.

### Statistical analysis

Numerical data are presented as medians with ranges, while categorical data as numbers with percentages. One-month drug exposure prevalence rates were calculated along with their exact (Clopper-Pearson) 95% confidence intervals (CI) (Newcombe 1998). To estimate the representativeness of collected controls in relation to the population of catchment areas, a comparison of general characteristics of individuals undergoing the interview and their exposure rates to topical ketoprofen with the expected distribution, based on census and IMS sales data obtained from individual areas in the period 2012–2013, were made. The assessment was done by comparing 95% CI for the difference between proportions or medians against fixed tolerances. These were:  $\pm 5\%$  for gender,  $\pm 5$  years for age distributions and  $\pm 1\%$  for topical ketoprofen exposure. Reproducibility of selected items of the questionnaire was assessed by calculating Cohen's kappa for nominal variables (Cohen 1960), and by one-way single measure intraclass correlation coefficient (ICC) for ordinal or continuous variables (McGraw and Wong 1996), together with their 95% CI. Values of Cohen's kappa and ICC greater than 0.60 indicate an acceptable reliability of questionnaire variables.

In the design of the study we estimated, based on IMS sales data, that the 1-month prevalence of exposure to NSAIDs was not lower than 0.5%. Hence a sample of about 900 controls (300 per centre) would have ensured a 95% CI total width equal or lower than 1% for a prevalence of no more than 0.5%. During the study, however, the number of controls had been adjusted per area based on relative ability to enrol patients.

Incidence rates were calculated, together with their exact 95% CI, by pooling the data in each region based on their relative sample size.

In order to summarize the study results in a single measure that takes into account the impact of individual drug exposure on the disease incidence, the population attributable risk (PAR) was used. PAR estimates the number of cases in the total population that are attributed to an exposure factor, taking into account both the risk ratio and the prevalence of exposure in the general underlying population. It can assume both positive and negative values, for risk or protective factors respectively, ranging from  $-100\%$  to  $100\%$ . In our study, the indirect method proposed by Cole and MacMahon (1971) was used. 95% CI for PAR was calculated by using the substitution method (Daly 1998), where the population-exposure was treated as a fixed factor while the 95% CI for the odds ratio (OR) was calculated by using exact mid-P estimate (Berry and Armitage 1995). When required, a continuity correction was applied in the computation of the OR and exposure prevalence (Cox 1970). Statistical analysis was performed using SPSS software, version 17.0 (SPSS, Chicago, IL).

### Results

From October 2012 to September 2013, a total of 920 controls were recruited, 370 (40.2%) in the Lombardy region (Italy), 300 (32.6%) in the Paris metropolitan area (France), and 250 (27.2%) in the Prague area (Czech Republic). This is consistent with the sample size estimation given in the design of the study. General data and main demographics of controls, by geographical region and overall, are reported in Table 1. The median age of subjects interviewed was 44 years ranging from 18 to 74 and 50.8% of them were women. The age and gender distribution was consistent with that of the underlying population in each area, with an overall difference of  $-0.07\%$  (95% CI,  $-3.30-3.16$ ) with the general population proportion of women and of 0 years (95% CI,  $-2-2$ ) with the population age distribution. The median BMI of controls was  $24.9 \text{ kg/m}^2$ ; most of people were workers (59.1%) or retired (19.0%) and with a high-school degree (55.3%). Here, 29.3% were smokers and 52.7% occasional drinkers, with slight variations among countries.

Table 2 reports lifetime history of skin conditions for controls. Most common skin diseases during the lifetime were: atopic dermatitis (2.9%), psoriasis (2.7%), and urticaria (2.5%). Three subjects (0.3%) reported an allergic reaction to topical ketoprofen during the lifetime, one of which was hospitalized (0.1%); six controls (0.7%) reported an allergic reaction to other topical NSAIDs during the lifetime and none of these was hospitalized.

**Table 1.** General data and main demographics of controls, by geographical region and overall.

	Geographical region							
	Lombardy (N = 370)		Paris area (N = 300)		Prague area (N = 250)		Total (N = 920)	
	n <sup>1</sup>	%	n <sup>1</sup>	%	n <sup>1</sup>	%	n <sup>1</sup>	%
Gender								
Female	187	50.5	157	52.3	123	49.2	467	50.8
Male	183	49.5	143	47.7	127	50.8	453	49.2
Age (years) Median (range)	45.0	18–74	44.0	18–74	42.5	18–74	44.0	18–74
18–34	104	28.1	94	31.3	74	29.6	272	29.6
35–54	136	36.8	117	39.0	95	38.0	348	37.8
55–74	130	35.1	89	29.7	81	32.4	300	32.6
BMI (kg/m <sup>2</sup> )								
Median (range)	24.4	14.4–50.9	24.8	14.0–49.8	26.2	16.7–76.4	24.9	14.0–76.4
<25.0	210	57.4	149	52.3	96	38.9	455	50.7
25.0–29.9	119	32.5	94	33.0	93	37.7	306	34.1
30.0	37	10.1	42	14.7	58	23.5	137	15.3
Marital status								
Married/common-law husband/wife	230	62.2	164	54.7	143	57.2	537	58.4
Unmarried	109	29.5	94	31.3	72	28.8	275	29.9
Divorced/widowed	29	7.8	41	13.7	35	14.0	105	11.4
Other	2	0.5	1	0.3	0	0.0	3	0.3
Occupational status								
Working	204	55.1	174	58.0	166	66.4	544	59.1
Student	12	3.2	12	4.0	15	6.0	39	4.2
Unemployed/searching for a job	27	7.3	37	12.3	8	3.2	72	7.8
Retired	77	20.8	53	17.7	45	18.0	175	19.0
Disability pension	9	2.4	6	2.0	4	1.6	19	2.1
Housewife/househusband	38	10.3	17	5.7	7	2.8	62	6.7
Other	3	0.8	1	0.3	5	2.0	9	1.0
Highest level of education								
Compulsory education not completed	49	13.3	8	2.7	1	0.4	58	6.3
Compulsory education	63	17.1	94	31.3	8	3.2	165	18.0
High school	206	55.8	115	38.3	187	74.8	508	55.3
First level degree	34	9.2	37	12.3	28	11.2	99	10.8
Second level degree	17	4.6	46	15.3	26	10.4	89	9.7
Smoking habits								
Smoker	93	25.1	99	33.0	78	31.2	270	29.3
Ex-smoker	70	18.9	66	22.0	51	20.4	187	20.3
Nonsmoker	207	55.9	135	45.0	121	48.4	463	50.3
Alcohol consumption								
Regular drinker	10	2.7	25	8.3	11	4.4	46	5.0
Occasional drinker	111	30.1	171	57.0	202	80.8	484	52.7
Ex-drinker	8	2.2	11	3.7	7	2.8	26	2.8
Non-drinker	240	65.0	93	31.0	30	12.0	363	39.5

<sup>1</sup>Numbers may not add up to the total due to missing data.

## Drugs exposure prevalence

Table 3 shows the estimated 1-month prevalence of exposure to selected medications in the control group, by the geographical region involved and overall. The 1-month prevalence of exposure to topical ketoprofen was 0.65% (95% CI, 0.24–1.42), ranging from 0% (95% CI, 0–0.99) for Lombardy and Prague (95% CI, 0–1.46) to 2.02%

(95% CI, 0.74–4.34) for Paris; for other topical NSAIDs it was 3.07% (95% CI, 2.05–4.41), ranging from 0% (95% CI, 0–1.47) for Prague to 8.22% (95% CI, 5.34–11.98) for Paris. The prevalence of exposure to systemic NSAIDs during the last month was 17.44% (95% CI, 15.02–20.07) and for other systemic drugs was 42.56% (95% CI, 39.33–45.84). The 1-month exposure rates to topical ketoprofen was quite consistent with the estimates derived from IMS



**Table 2.** Lifetime history of skin conditions for controls, by geographical region and overall.

	Geographical region							
	Lombardy (N = 370)		Paris area (N = 300)		Prague area (N = 250)		Total (N = 920)	
	n*	%	n*	%	n*	%	n*	%
<b>Skin diseases</b>								
Atopic dermatitis	8	2.2	7	2.3	12	4.8	27	2.9
Psoriasis	7	1.9	14	4.7	4	1.6	25	2.7
Contact dermatitis	3	0.8	2	0.7	9	3.6	14	1.5
Urticaria	1	0.3	19	6.3	3	1.2	23	2.5
Polymorphous light eruptions	0	0.0	1	0.3	7	2.8	8	0.9
Other photosensitivity reactions	0	0.0%	4	1.3%	0	0.0	4	0.4
Herpes simplex	0	0.0%	5	1.7%	7	2.8	12	1.3
Vitiligo	2	0.5%	1	0.3%	1	0.4	4	0.4
Other skin diseases	1	0.3%	85	28.3%	11	4.4	97	10.5
<b>Diseases predisposing to photosensitivity</b>								
Systemic lupus erythematosus	0	0.0	1	0.3	1	0.4	2	0.2
Other rheumatic disease	2	0.5	4	1.3	1	0.4	7	0.8
Allergic reaction to topical ketoprofen	1	0.3	2	0.7	0	0.0	3	0.3
Requiring hospitalization	1	0.3	0	0.0	0	0.0	1	0.1
Lifetime allergic reaction to other topical NSAIDs	2	0.5	2	0.7	2	0.8	6	0.7
Requiring hospitalization	0	0.0	0	0.0	0	0.0	0	0.0
Lifetime adverse effect to other medications	27	7.3	86	30.4	44	17.6	157	17.4
Requiring hospitalization	7	1.9	15	5.3%	6	2.4	28	3.1

<sup>1</sup>Unknown and missing data were excluded from the computation.

sales data, with an overall difference of 0.39% (95% CI, -0.02–1.15) with the general population estimate.

### Questionnaire validation

In order to evaluate questionnaire reproducibility, a random sample of 32 controls who had taken part in the study underwent a second interview by the same interviewer after about a week (median 8 days, ranging from 4 to 18). The overall agreement on different questionnaire items was good, ranging from 0.64 (95% CI, 0.39–0.81) for skin diseases during the lifetime to 1 (95% CI, 0.999–1) for other variables, including drugs exposure specific questions.

### Incidence of severe photosensitivity reactions

Table 4 shows the incidence rate of severe photosensitivity reactions overall and by geographical region and in relation to each suspected drug. A total of 8 severe photosensitivity cases were reported in the population aged 18–74 years of the 3 geographical areas during the 1-year surveillance period, with an overall incidence rate of 4.81 cases per 10 million person-years (95% CI, 2.07–9.48), ranging from 0 (95% CI, 0–38.48) for Prague to 2.73 (95% CI, 0.33–9.86) for Lombardy, and to 7.20 (95% CI,

2.64–15.66) for Paris. The incidence rate of cases linked to topical ketoprofen was 0.61 per 10 million person-years (95% CI, 0.01–3.35), ranging from 0 for Paris (95% CI, 0–4.42) and Prague (95% CI, 0–38.48) to 1.36 (95% CI, 0.03–7.61) for Lombardy. The incidence rate of reactions linked to other topical NSAIDs as well as to systemic NSAIDs in all regions involved was 0 per 10 million person-years (95% CI, 0–2.21), while the incidence of cases linked to other systemic or topical drugs was 4.21 per 10 million person-years (95% CI, 1.69–8.68).

Based on data from participating pharmacovigilance databases, we estimated that 1 out of 7 reported photosensitivity reactions, of any grade, required hospitalization (data not shown). This proportion changed to 1 out of 5 for cases linked to topical ketoprofen.

### Population attributable risk

PAR related to topical ketoprofen use and to other drugs of interest is reported in Table 5. Based on our data, we estimated that the overall PAR for severe photosensitivity reactions leading to hospitalization linked to topical ketoprofen in the population aged 18–74 years of the 3 geographical areas was 11.92% (95% CI, -0.12–52.99) with an OR of 21.69 (95% CI, 0.82–173.30), ranging from 4.72% (95% CI, -2.06–42.66) in Paris to 27.01% (95% CI, 0.43–100) in Lombardy. The PAR for other topical

**Table 3.** One-month drug exposure prevalence for controls, by geographical region and overall.

	Geographical region						Total	
	Lombardy		Paris area		Prague area			
	%*	95% CI	%*	95% CI	%*	95% CI	%*	95% CI
Topical ketoprofen	0	0–0.99	2.02	0.74–4.34	0	0–1.46	0.65	0.24–1.42
Other topical NSAIDs	1.08	0.30–2.74	8.22	5.34–11.98	0	0–1.47	3.07	2.05–4.41
Other topical medications	0.27	0.01–1.50	9.25	6.18–13.16	1.20	0.25–3.47	3.40	2.32–4.79
Systemic NSAIDs	21.35	17.28–25.88	21.45	16.86–26.64	6.88	4.06–10.79	17.44	15.02–20.07
Ketoprofen	6.76	4.42–9.81	3.51	1.70–6.36	0	0–1.48	3.88	2.72–5.36
Other	14.59	11.16–18.61	17.19	13.00–22.08	6.88	4.06–10.79	13.30	11.15–15.70
Other systemic drugs	22.16	18.03–26.74	69.05	63.42–74.29	41.6	35.42–47.98	42.56	39.33–45.84

CI, confidence interval.

\*Unknown and missing data were excluded from the computation.

**Table 4.** Severe photosensitivity incidence rates (per 10 million person-years) in total and linked to exposure to different drugs exposure, by geographical region and overall.

	Geographical region						Total (N = 16,623,355)	
	Lombardy (N = 7,325,746)		Paris area (N = 8,338,986)		Prague area (N = 958,623)			
	n	r (95% CI)	n	r (95% CI)	n	r (95% CI)	n	r (95% CI)
Overall	2	2.73 (0.33–9.86)	6	7.20 (2.64–15.66)	0	0 (0–38.48)	8	4.81 (2.07–9.48)
Topical ketoprofen	1	1.36 (0.03–7.61)	0	0 (0–4.42)	0	0 (0–38.48)	1	0.61 (0.01–3.35)
Other topical NSAIDs	0	0 (0–5.04)	0	0 (0–4.42)	0	0 (0–38.48)	0	0 (0–2.21)
Systemic NSAIDs	0	0 (0–5.04)	0	0 (0–4.42)	0	0 (0–38.48)	0	0 (0–2.21)
Ketoprofen	0	0 (0–5.04)	0	0 (0–4.42)	0	0 (0–38.48)	0	0 (0–2.21)
Other	0	0 (0–5.04)	0	0 (0–4.42)	0	0 (0–38.48)	0	0 (0–2.21)
Other systemic or topical drugs	1	1.36 (0.03–7.61)	6	7.20 (2.64–15.66)	0	0 (0–38.48)	7	4.21 (1.69–8.68)

n, number of cases; r, incidence rates (per 10 million person-years); CI, confidence interval.

NSAIDs was 2.47% (95% CI, –3.17–29.99) and the OR equal to 1.82 (95% CI, 0–14.94), ranging from –1.31% (95% CI, –8.96–35.13) in Paris to 14.18% (95% CI, –1.09–79.32) in Lombardy; for systemic ketoprofen it was 1.67% (95% CI, –4.04–29.22) with an OR of 1.44 (95% CI, 0–11.64); for other systemic or topical drugs it was 77.69% (95% CI, 14.00–98.89) and the OR equal to 8.92 (95% CI, 1.37–202.81).

## Discussion

Our pilot study conducted in selected European areas, showed that the incidence of photosensitivity reactions leading to hospitalization was low for all the potential causative factors, including topical ketoprofen, with estimates lower than previously reported (Baudot et al. 1998;

**Table 5.** Population attributable risk (PAR) linked to exposure to different drugs, by geographical region and overall.

	Geographical region			
	Lombardy PAR (95% CI)	Paris area PAR (95% CI)	Prague area PAR (95% CI)	Total PAR (95% CI)
Topical ketoprofen	27.01% (0.43–100)	4.72% (–2.06–42.66)	NC	11.92% (–0.12–52.99)
Other topical NSAIDs	14.18% (–1.09–79.32)	–1.31% (–8.96–35.13)	NC	2.47% (–3.17–29.99)
Systemic ketoprofen	10.36% (–7.25–76.39)	3.45% (–3.64–39.86)	NC	1.67% (–4.04–29.22)
Other systemic or topical drugs	35.54% (–25.65–96.79)	73.84% (–45.56–100)	NC	77.69% (14.00–98.89)

Some drug categories were excluded since PAR was not computable. NC, not computable; CI, confidence interval.

Naldi *et al.* 1999; Veyrac *et al.* 2002; Diaz *et al.* 2006; Noize *et al.* 2010).

There is a paucity of data about the incidence of severe photosensitivity reactions in the general population. To the best of our knowledge, only two surveys allowed to calculate the reporting rate of drug-induced photosensitivity reactions on a given population base. The first study was an analysis of spontaneous reports in Italy in the period 1996–1997 (Naldi *et al.* 1999). The reporting rate of photosensitivity reactions (limited to reactions classified as “severe”, i.e., leading to hospitalization) was 0.09 per 100,000 inhabitants per year. The second survey was conducted in the Biskay territory in Spain in the period 1996–2001 and was restricted to NSAIDs. A total of 83 photoallergic reactions attributed to NSAIDs were observed over the analyzed period, with a rate of about 1.2 per 100,000 per year (Diaz *et al.* 2006). Ketoprofen accounted for the vast majority of these reactions. A third study conducted in France only focused on reactions to ketoprofen with rates of any reaction ranging from 1.3 to  $2.8 \times 100,000$  (Veyrac *et al.* 2002).

PAR indicates the proportion of cases of a disease attributed to a given exposure in the population. Its measure depends on the prevalence of exposure to a causative factor and the degree of association between the exposure and the disease. In population terms, a rare exposure associated with a high risk may be less serious, in the total number of related events, than a very common exposure with a lower risk. Our study showed that the PAR linked to topical ketoprofen was almost 12%, indicating that about one in eight cases of severe photosensitivity reactions is attributable to the drug. The risk ratio was higher compared to other NSAIDs and drugs of interest.

In spite of some attempts at standardization, there are no shared criteria for the diagnosis of photosensitivity reactions. In our study, the severity of reactions was judged based on hospitalization. This reduced the number of total cases collected, since hospitalization policies change over time and between countries. We estimated that about 1 out of 5 cases of photosensitivity reactions due to ketoprofen use was hospitalized.

In our study, information on drug exposure among patients admitted for acute conditions not linked with underlying chronic diseases, using questionnaires similar to those proposed by the Slone Epidemiology Unit (Slone *et al.* 1977), was taken as a reliable proxy for the prevalence of drug exposure in the general population. Comparisons made in the context of studies such as the SCAR and the EuroSCAR projects have confirmed that the prevalence of drug exposure among hospital controls admitted for acute conditions are comparable to those obtained from the general population (Kelly *et al.* 1995;

Auquier-Dunant *et al.* 2002; Mockenhaupt *et al.* 2008). In our study, the prevalence of exposure to topical ketoprofen was found to be in accordance with the national sales data.

Our study was a pilot one. Based on collected data, it could be computed that at least 26 cases should be collected with a case : control ratio of 1:100 (2600 controls) in order to have enough power to reduce the 95% CI width of the PAR estimate to 30% or lower. The feasibility of a large European study clearly depends on the number of cases that one could collect during a reasonably short period of time, and, on the number of controls recruited per case. The rate of hospitalization for photosensitivity reactions appear to be quite low. Consequently, the main study as designed in the protocol was deemed not feasible. As an alternative to a hospital-based case-control study, one may consider to conduct the study in the outpatient setting. In such a community-based study, other factors such as cross-sensitization (e.g. among ketoprofen and octocrylene) and poly-sensitization could be also assessed.

## Conclusions

To summarize, we documented that the incidence of severe photosensitivity reactions leading to hospitalization was low and that among topical NSAIDs, topical ketoprofen was the leading cause even if it accounted for a limited number of cases of the reaction. Our study was a pilot one. A different study design focusing on the outpatient setting could better estimate the incidence of photosensitivity reactions in the general population.

## Acknowledgements

We thank all the nurses and physicians who contributed to the study and the patients whether they were cases or controls. In particular: Cynthia Haddad and Colin Audrey (Department of Dermatology, Hôpital Henri-Mondor, Créteil - France), Luigina Vecchi and Maurizio Cortinovis (Bergamo Sanità social cooperative, Nembro - Italy), Filip Rob and Mirka Brejchova (Department of Dermatology, 2nd Faculty, Charles University and Hospital Bulovka, Prague - Czech Republic).

## Author Contributions

Cazzaniga and Lecchi had full access to the data and took part in study coordination. Cazzaniga was responsible for data analysis. Cazzaniga, Lecchi, and Naldi contributed to the writing of the article. Naldi, Kürzinger, Auclert, Gori, Chosidow, and Hercogova were responsible for critical review of the work.



## Disclosures

ML. Kürzinger and L. Auclert are employees of Sanofi, M. Gori is a medical doctor at Menarini Ricerche S.p.A. Luigi Naldi acted as a consultant for Bayer, Menarini, and Sanofi. Simone Cazzaniga received consultation fees from Abbvie, Janssen-Cilag and Difa Cooper. Sanofi-Aventis Groupe, Menarini Industrie Farmaceutiche Riunite S.r.l and Bayer S.p.A. were all manufacturers of topical ketoprofen. No declarations were made for each case as there was nothing to declare.

## References

- Auquier-Dunant A, Mockenhaupt M, Naldi L, Correia O, Schröder W, Roujeau JC (2002). Severe Cutaneous Adverse Reactions. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. *Arch Dermatol* 138: 1019–1024.
- Bagheri H, Lhiaubet V, Montastruc J, Chouini-Lalanne N (2000). Photosensitivity to ketoprofen: mechanisms and pharmacoepidemiological data. *Drug Saf* 22: 339–349.
- Baudot S, Milpied B, Larousse C (1998). Cutaneous side effects of ketoprofen gels: results of a study based on 337 cases. *Thérapie* 53: 137–144.
- Berry G, Armitage P (1995). Mid-P confidence intervals: a brief review. *Statistician* 44: 417–423.
- Cantisani C, Grieco T, Faina V, Mattozzi C, Bohnenberger H, Silvestri E, et al. (2010). Ketoprofen allergic reactions. *Recent Pat Inflamm Allergy Drug Discov* 4: 58–64.
- Cazzaniga S, Lecchi S, Bruze M, Chosidow O, Diepgen T, Gonçalves M, et al. (2015). Development of a clinical score system for the diagnosis of photoallergic contact dermatitis using a consensus process: item selection and reliability. *J Eur Acad Dermatol Venereol* 29: 1376–1381.
- Cohen J (1960). A coefficient of agreement for nominal scales. *Educ Psychol Meas* 20: 37–46.
- Cole P, MacMahon B (1971). Attributable risk percent in case-control studies. *Br J Prev Soc Med* 25: 242–244.
- Cox DR (1970). The continuity correction. *Biometrika* 57: 217–219.
- Daly LE (1998). Confidence limits made easy: interval estimation using a substitution method. *Am J Epidemiol* 147: 783–790.
- Diaz RL, Gardezabal J, Manrique P, Ratón JA, Urrutia I, Rodríguez-Sasiain JM, et al. (2006). Greater allergenicity of topical ketoprofen in contact dermatitis confirmed by use. *Contact Dermatitis* 54: 239–243.
- Durrieu G, Mazau B, Jégu J, Lapeyre-Mestre M, Delord JP, Montastruc JL (2013). Drugs and cancer: an analysis of the French Pharmacovigilance Database. *Thérapie* 68: 149–154.
- Galfrascoli E, Magni E, Panciroli C, Bonfatti C, Cerveri G, Boschiero AM, et al. (2012). Improving pharmacovigilance in psychiatry. *Eur J Hosp Pharm* 19: 110–111.
- Gamba C, Schroeder J, Citterio A, Cazzaniga S, Rivolta AL, Vighi G (2014). Surveillance of severe cutaneous drug reactions: experience REACT-Lombardia. *Recenti Prog Med* 105: 379–384.
- Kalton G (1983). *in* Pp. 19–23. Introduction to survey sampling. SAGE University Paper series on Quantitative Applications in the Social Sciences, vol.35. SAGE Publications Inc, Beverly Hills and London.
- Kelly JP, Auquier A, Rzany B, Naldi L, Bastuji-Garin S, Correia O, et al. (1995). An international collaborative case-control study of severe cutaneous adverse reactions (SCAR). Design and methods. *J Clin Epidemiol* 48: 1099–1108.
- Matthieu L, Meuleman L, Van Hecke E, Blondeel A, Dezfoulian B, Constandt L, et al. (2004). Contact and photocontact allergy to ketoprofen. The Belgian experience. *Contact Dermatitis* 50: 238–241.
- McGraw KO, Wong SP (1996). Forming inferences about some intraclass correlation coefficients. *Psychol Methods* 1: 30–46.
- Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, et al. (2008). Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. *J Invest Dermatol* 128: 35–44.
- Naldi L, Conforti A, Venegoni M, Troncon MG, Caputi A, Ghiotto E, et al. (1999). Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. *Br J Clin Pharmacol* 48: 839–846.
- Newcombe RG (1998). Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med* 17: 857–872.
- Noize P, Bénard-Larivière A, Aulois-Griot M, Moore N, Miremont-Salamé G, Haramburu F (2010). Cutaneous adverse effects of ketoprofen for topical use: clinical patterns and costs. *Am J Clin Dermatol* 11: 131–136.
- Slone D, Shapiro S, Miettinen O (1977). Case-control surveillance of serious illnesses attributable to ambulatory use of drugs. Pp. 59–70 *in* F. Colombo, D. Slone, S. Shapiro and G. Tognoni, eds. *Epidemiological evaluation of drugs*. Elsevier/North Holland Biomedical Press, Amsterdam.
- Veyrac G, Paulin M, Milpied B, Bourin M, Joliet P (2002). Results of a French nationwide survey of cutaneous side effects of ketoprofen gel reported between September 1996 and August 2000. *Thérapie* 57: 55–64.