Incidence of Mucocutaneous Reactions in Children Treated With Niflumic Acid, Other Nonsteroidal Antiinflammatory Drugs, or Nonopioid Analgesics

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ABSTRACT. *Background and Objective.* **Results from a relatively small case-control study recently showed that niflumic acid increases the risk of serious mucocutaneous reactions in children. As a consequence, the Italian Ministry of Health sent a "Dear Doctor" letter in June 2001 to warn pediatricians about the alleged adverse effects. The objective of this study was to estimate and compare the incidence of mild and severe mucocutaneous reactions among children using niflumic acid, other nonsteroidal antiinflammatory drugs (NSAIDs), or nonopioid analgesics.**

Design. **Retrospective cohort study.**

Setting. **Italy is one of the few countries in which a specific primary care system is devoted to children up to 14 years of age: every child is registered at birth and receives free medical care from 1 of the ~6000 family pediatricians working for the National Health Service. This study was conducted with the Pedianet network of Italian family pediatricians who use computerized electronic patient records for routine care; 185 pediatricians participated in the study. The patient records comprise information on demographics, diagnoses, symptoms, prescriptions, referrals, laboratory examinations, and hospitalizations.**

Participants. **Children aged 0 to 14 years and registered with 1 of the collaborating pediatricians between January 1, 1998, and May 31, 2001.**

Main Outcome Measures. **The incidence rate of severe (hospitalized or referred) and mild mucocutaneous reactions (exanthema, disseminated or localized pruritus, urticaria, angioedema, fixed eruption, dermatitis, erythema multiforme, vesicles, bullae, pustules, toxic epidermal necrolysis, purpura, and vasculitis) was estimated during use of niflumic acid, other NSAIDs, or nonopioid analgesics. For each episode of drug use, the following covariates were assessed: age, gender, region, year, indication for study drug, use of antibiotics, antimycotic agents, glucocorticoids, and other NSAIDs. Multivariate Poisson regression analysis was used to estimate the adjusted relative risk of mucocutaneous disorders during use of niflumic acid compared with use of other NSAIDs or use of acetaminophen alone.**

Results. **The population included 193 727 children, 45 351 of whom received at least 1 of the study drugs. The most frequently prescribed drugs were niflumic acid, acetaminophen, and propionic acid derivatives (ketoprofen and flurbiprofen). Users of niflumic acid (n = 32 150) were younger and slightly more often had otitis media or upper respiratory tract infections as an indication compared with the other NSAIDs. During use of the various study drugs we identified 1451 mild mucocutaneous events and 42 severe reactions. The incidence rates of severe and mild mucocutaneous reactions after the administration of any study drug were 10.3 per 100 000 exposure person-days and 3.7 per 1000 exposure person-days, respectively. Both incidence rates decreased strongly with increasing age. In comparison with other NSAIDs, the adjusted relative risks of niflumic acid were 0.5 (95% confidence interval: 0.23–1.27) for severe and 0.9 (95% confidence interval: 0.79–1.11) for mild mucocutaneous reactions. The use of acetaminophen as a reference category instead of other NSAIDs, restriction of the children to those who received NSAIDs for respiratory tract infections, or restriction to those who did not use antibiotics never revealed an increased risk of serious or mild mucocutaneous reactions during use of niflumic acid.**

Conclusions. **In comparison with other NSAIDs or acetaminophen, niflumic acid is not associated with an increased risk of severe or mild mucocutaneous reactions in children. This was true for the different age groups and various types of mucocutaneous reactions, was independent of the concomitant use of antibiotics, and was not sensitive to changes in our assumptions regarding exposure and outcomes.** *Pediatrics* **2005;116:e26–e33. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0040;** ***niflumic acid, NSAIDs, analgesics, mucocutaneous reactions, children, cohort.***

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ABBREVIATIONS. NSAID, nonsteroidal antiinflammatory drug; FP, family pediatrician; RR, relative risk; CI, confidence interval; OTC, over-the-counter.

It was recently alleged that niflumic acid, the only nonsteroidal antiinflammatory drug (NSAID) that was licensed for use in small children in Italy in 2001, increases the risk of mucocutaneous reactions in children.[1]

It is known that NSAIDs may cause dermatological reactions ranging from rash and urticaria to severe reactions such as Lyell's syndrome and Stevens-Johnson syndrome.[2,3] These adverse drug reactions are of public health relevance because of the widespread use of NSAIDs in both pediatric and adult clinical practice. The NSAIDs that are prescribed most frequently to children in Italy are niflumic acid, nimesulide, and propionic acid derivatives.[4] In addition to Italy, niflumic acid is available for children and adults in France, Spain, and Portugal and only for adults in Belgium, Luxemburg, Switzerland, Germany, and Greece.[1]

An Italian hospital-based case-control study of adverse drug reactions in children found an almost fourfold excess risk of severe mucocutaneous reactions among the users of niflumic acid and its β-morpholinoethyl ester morniflumate (hereinafter aggregated with niflumic acid).[1] As a consequence, the Italian Ministry of Health sent a "Dear Doctor" letter in June 2001 to warn pediatricians about the alleged adverse effects. However, the results of that study have to be interpreted very cautiously: the authors took nonuse as the reference exposure group and, as they acknowledged, were unable to control for potential confounding factors except for the use of other drugs. Furthermore, case-control studies are susceptible to bias, especially if little is known about the incidence of the disease in question, and questionnaires are used to collect retrospective data.

To assess the association between niflumic acid and mucocutaneous reactions in a more appropriate context, this retrospective cohort study of a population of children registered with the family pediatricians (FPs) participating in the Pedianet network in Italy studied the pattern of use of NSAIDs in pediatric primary care and estimated the incidence of mucocutaneous reactions during exposure to different niflumic acid, other NSAIDs, and nonopioid analgesics.

METHODS

Setting

Italy is 1 of the few countries in which a specific primary care system is devoted to children up to 14 years of age; every child is registered at birth and receives free medical care from 1 of the ~6000 FPs working for the National Health Service.

Our retrospective population-based cohort study was based on Pedianet, a network of FPs participating in a common epidemiologic and clinical research project concerning the care of children.[5,6] The participating FPs are experienced users of the same electronic patient record software; the data contained in their records are generated from routine patient encounters and include diagnoses, symptoms, prescriptions (regardless of National Health Service reimbursement), certificates, medical examinations, referrals, and hospitalizations.

The source population for this study included all of the children registered with 1 of the 185 participating FPs during the study period (January 1, 1998, through May 31, 2001). The data for each child were collected from the start of the study period (or the date of FP registration, if later) until the occurrence of a mucocutaneous reaction or death, until the patient was transferred or reached the age of 15 years, or until the end of the study period. The collected data were handled anonymously as required by Italian privacy law.

Drug Exposure

We identified all the children in the source population who had received at least 1 prescription of an NSAID (indomethacin, sulindac, diclofenac, fentiazac, acemetacin, proglumethacin, ketorolac, diclofenac + misoprostol, cinnoxicam, piroxicam, tenoxicam, droxicam, meloxicam, furprofen, ibuprofen, naproxen, ketoprofen, flurbiprofen, tiaprofenic acid, mefenamic acid, amtolmetin, nabumetone, niflumic acid, nimesulide, morniflumate), a nonopioid analgesic including acetaminophen or acetylsalicylic acid derivatives, or pyrazolinone derivatives. To compare effects among drug classes, we separately considered niflumic acid/morniflumate, non–niflumic acid NSAIDs, acetaminophen, and nonacetaminophen nonopioid analgesics (acetylsalicylic acid and pyrazolinones).

Exposure to the study drugs was expressed as person-time and characterized by using the specific active principles (alone or in combination) and other variables of interest. Mutually exclusive treatment periods of current use were defined by applying the following rules: (1) a fixed duration of 5 days was assigned to all NSAID prescriptions (mean prescribed duration); (2) prescriptions for different study drugs issued on the same day were considered "combinations"; and (3) if a new study drug was prescribed during treatment with a previously prescribed study drug, it was assumed that the first treatment ended on the date of the new prescription. Each period of current use started on day 1 of the treatment period and ended (1) after 5 days, (2) on the date of the start of a treatment period with another NSAID, (3) on the occurrence of a mucocutaneous reaction, or (4) at the end of follow-up. A child could contribute information to different exposure categories if he/she was prescribed >1 drug during the study period. Nonexposed person-time during the study period was not considered.

Outcomes

The outcome was the occurrence of the possibly drug-induced mucocutaneous reactions described in the literature: exanthema, disseminated or localized pruritus, urticaria, angioedema, fixed eruption, dermatitis, erythema multiforme, vesicles, bullae, pustules, toxic epidermal necrolysis, purpura, and vasculitis.[7–9] The reactions were classified as severe if they led to (1) hospital admission, (2) an emergency-department visit, or (3) referral to specialist consultation. The reactions that were dealt with in primary care were classified as mild.

Potential outcomes were identified by (1) searching the FP electronic records for diagnoses and hospitalizations with *International Classification of Diseases, Ninth Revision*, codes of 690, 691, 693, 694, 695, 698, 708, 287, 528.2, or 528.0, and (2) searching the same records for diagnoses, signs, or symptoms as free text (a list of these search terms is available on request). All events of interest had to have occurred within the risk window (ie, the estimated duration of drug use plus a carryover period of 30 days to account for delayed notifications). Events occurring before exposure or >30 days after exposure were not considered to limit confounding by indication. To validate the completeness of case ascertainment of severe outcomes (hospitalizations) in the FPs' computerized records, we sought the computerized hospitalization files relating to all children registered with the participating FPs during the study period from the local health authorities. These records were linked on date of birth, gender, and FP and used to extract the discharge records with a diagnosis of any of the study outcomes.

For each identified case of severe mucocutaneous reaction, we asked the FP to validate the diagnosis and date of occurrence. The reactions were categorized as (1) exanthema, erythema, eruptions, rash, (2) urticaria, (3) vasculitis, thrombocytopenia, (4) stomatitis, and (5) other forms of dermatitis. All mild reactions were reviewed by 2 physicians blinded to the exposure. The reactions probably caused by standard infectious diseases in children (mea-

sles, mumps, fifth disease, etc) and cases of atopic dermatitis were not considered outcomes.

Statistical Analysis

The incidence rate of mucocutaneous reactions was calculated by using the number of cases as the numerator and the person-time of treatment duration (without carryover) as the denominator. Potential risk factors such as age, gender, indication, the concomitant use of antibiotics, antimycotic or antiviral agents, and previous use of study drugs were taken into account. The demographic information was obtained from the patient files, the indications from the reason-for-access field completed on the same date as that of the drug prescription, and concomitant drug use from the prescription records (coded and free text).

The risk of mucocutaneous reactions was estimated by using multivariate Poisson regression analysis. Sensitivity analyses were made to investigate the potential effects of the misclassification of exposure and outcome. All of the analyses were made by using SPSS 11 (SPSS, Chicago, IL) and SAS/PC 6 (SAS Institute, Cary, NC).

RESULTS

The source population included 193 727 children 0 to 14 years old who were followed for an average of 2 years (total follow-up time: 397 694 person-years): 45 351 (23.4%) received at least 1 of the 84 609 prescriptions for the various study drugs, with 34% of them receiving >1 prescription.

Use

The most frequently prescribed drugs were niflumic acid, acetaminophen, and propionic acid derivatives (Table 1). Acetaminophen was prescribed mainly to neonates and toddlers but was frequently also prescribed to older children (Fig 1). The prescription of niflumic acid was concentrated among children 1 to 6 years old. Morniflumate was used predominantly by children ≥4 years old. The prescription of propionic acid derivatives started to increase at the age of ~3 years and subsequently remained at the same level. Use of non–niflumic acid NSAIDs was very limited in children <8 years old but increased steadily after this age.

TABLE 1. Prescriptions and Users of Different Classes of Study Drugs and the Most Frequently Used Individual Drugs Within Each Class

Drugs (Class and Name)	Prescriptions, *n* (%)	Users, *n* (%)
NSAIDs		
Acetic acid derivatives	55 (0.1)	48 (0.1)
Diclofenac	42	41
Oxicam derivatives	133 (0.2)	126 (0.3)
Piroxicam	129	123
Proprionic acid derivatives	15 654 (18.5)	11 216 (24.7)
Ketoprofen	10 445	7471
Flurbiprofen	5054	3900
Phenamate derivatives	1 (0.0)	1 (0.0)
Other NSAIDs*	5092 (6.0)	4110 (9.1)
Nimesulide	4677	3760
Nilfumic acid derivatives	32 150 (38.0)	21 384 (47.2)
Niflumic acid	26 681	17 824
Morniflumate	5469	4260
Other analgesics		
Acetylsalicylic acid derivatives	1421 (1.7)	1246 (2.7)
Acetylsalicylic acid	684	612
Imidazolsalicylate	592	498
Pyrazolinone derivatives	3014 (3.6)	2267 (5.0)
Metamizole	1266	1015
Propyphenazone combinations	1745	1255
Aceto anilide derivatives	27 089 (32.0)	17 292 (38.1)
Acetaminophen	21 918	14 256
Combinations	5156	4063
Total	84 609 (100)	45 351 (100)

* Excluding niflumic acid derivatives.

There were many differences between niflumic acid users and the users of other NSAIDs or analgesics: they were younger; a higher proportion had used another NSAID in the previous 30 days; and they more frequently presented with an indication for upper respiratory tract infection and concomitant antibiotic treatment (Table 2).

Incidence of Mucocutaneous Reactions

We identified 55 potentially severe mucocutaneous reactions from the FP electronic records, 42 of which were retained after validation (22 cases of urticaria, 12 of erythema/rash, 7 of vasculitis/purpura/thrombocytopenia, and 1 of stomatitis). No cases of Lyell's syndrome or Stevens-Johnson syndrome were observed. Eighteen children were admitted to a hospital, 17 were seen in emergency departments and discharged within 24 hours, and 7 were referred to a specialist. The computerized hospital records of all children relating to 76 FPs (41%) were searched for the outcomes. Only 4 potential mucocutaneous reactions occurring during the risk window were identified, but only 1 was judged to be a valid outcome; the 4 potential cases had also been identified in the FP's electronic records.

The incidence of severe mucocutaneous reactions after the administration of any study drug was 10.3 per 100 000 person-days and decreased from 13.5 among preschoolers to 0 after the age of 9 years (Table 3). Factors other than age showed a nonstatistically significant association.

In addition to severe reactions, 1451 valid mild mucocutaneous events were identified (491 cases of erythema/rash, 392 of urticaria, 419 of stomatitis, 21 of thrombocytopenia/vasculitis/purpura, and 128 of other types of dermatitis). The incidence rate of mild mucocutaneous reactions after the administration of any study drug was 3.7 per 1000 person-days and was associated with age, geographic area, the concomitant use of antimycotic and antiviral agents, and specific indications (Table 3). The age-specific incidence rates were consistent among the users of different study drug classes except for the extreme age groups, for which the data were sparse (Fig 2).

Drug-Specific Relative Risks

In comparison with other NSAIDs, the risk of severe mucocutaneous reactions to niflumic acid was lower but not statistically significant (age-adjusted relative risk [RR]: 0.5) (Table 4). The RR for niflumic acid (0.7) was influenced to some extent by the children's age (RR: 0.7; 95% confidence interval [CI]: 0.2–2.2) among children ≤3 years old and 0.2 (95% CI: 0.0–1.6) among older children. An analysis restricted to the children with an indication of respiratory tract infection yielded an age-adjusted RR of 0.4 (95% CI: 0.1–1.4). Exclusion of children who concomitantly used antibiotics yielded an age-adjusted RR of 0.4 (95% CI: 0.1–1.4). The restriction of the outcome to hospitalized patients led to an age-adjusted RR of

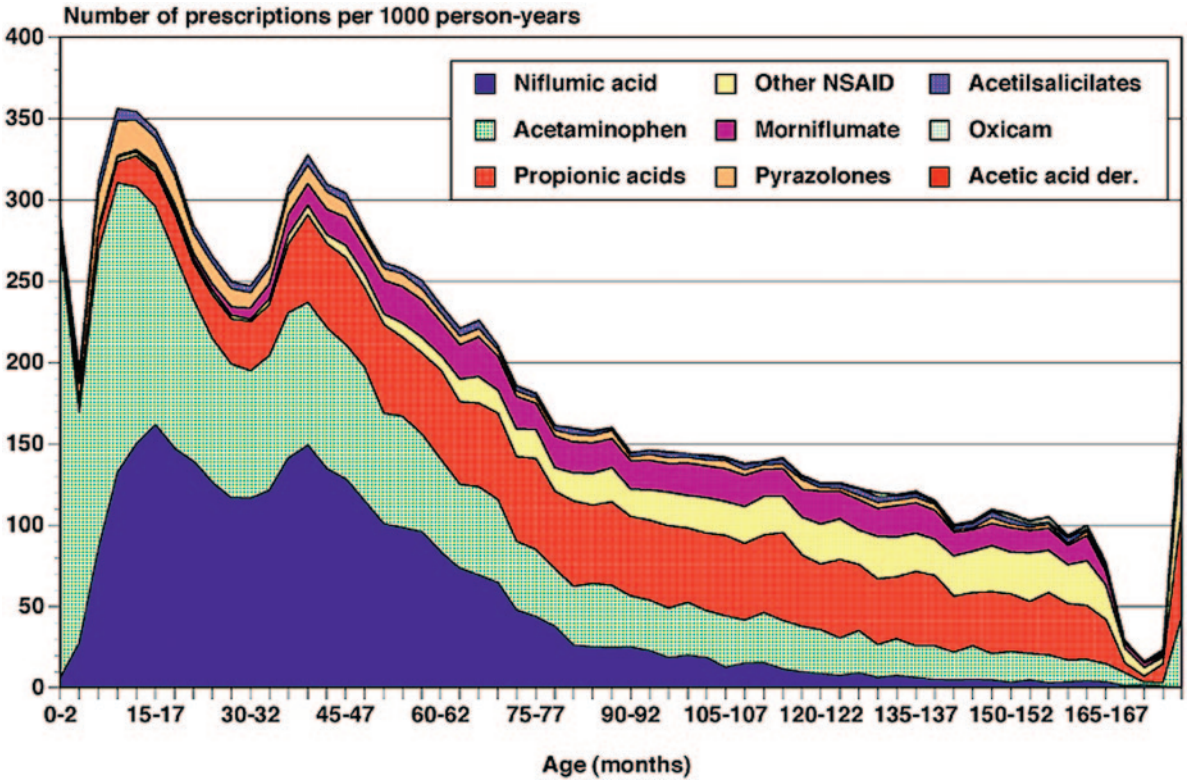

Fig 1. Cumulative use of different study drugs according to active principles and age (in months), expressed as the number of prescriptions per 1000 person-years in a cohort of 45 351 Italian children: 1998–2001.

0.6 (95% CI: 0.1–3.1). The use of acetaminophen instead of other NSAIDs as the reference category yielded an age-adjusted RR of 0.7 (95% CI: 0.3–1.7).

In the analysis of mild mucocutaneous reactions, the crude RR indicated an increased risk associated with acetaminophen (RR: 1.7; 95% CI: 1.4–1.9) and niflumic acid (RR: 1.2; 95% CI: 1.1–1.4), which were the drugs most frequently prescribed to the youngest children. However, these differences disappeared in the multivariate analysis, which showed an adjusted RR of 0.9 for niflumic acid and 1.1 for acetaminophen. Using acetaminophen rather than other NSAIDs as the reference group yielded an adjusted RR of 0.8 (95% CI: 0.7–0.9), which indicates a 20% lower risk of reactions associated with the use of niflumic acid. Gender and age did not modify the relationship between the use of niflumic acid and the occurrence of mild mucocutaneous reactions. In comparison with non–niflumic acid NSAIDs, the adjusted RRs of the specific types of mucocutaneous reactions associated with the use of niflumic acid were 1.1 for erythema/rash, 1.0 for urticaria, 1.5 for other forms of dermatitis, 1.0 for thrombocytopenia/vasculitis/purpura, and 0.7 for stomatitis (none were statistically significant).

The concomitant use of any antibiotic with any NSAID prescription was associated with a small risk of mild erythema/rash (RR: 1.2; 95% CI: 1.0–1.5) and urticaria (RR: 1.4; 95% CI: 1.2–1.8). Penicillins were particularly associated with mild erythema/rash (RR: 1.6; 95% CI: 1.2–2.0) and urticaria (RR: 1.4; 95% CI: 1.1–1.8). In comparison with other NSAIDs, the adjusted RR of mild mucocutaneous reactions during the use of niflumic acid was 1.0 (95% CI: 0.7–1.3) in the children not receiving concomitant antibiotics and 0.9 (95% CI: 0.8–1.2) in those who were.

Sensitivity Analyses

A number of sensitivity analyses were made to verify whether a change in the study's assumptions or definitions influenced the results: in all cases, the changes in the estimated RR were minimal and not statistically significant. The results of the most important of these analyses are described below.

To investigate the possibility of a bias induced by our definition of exposure (5 days for all drugs), we used an alternative drug-specific exposure time estimated as the legend duration and based on the number of units prescribed and available in the commercial packages (despite the prescribed duration). On the basis of these calculations, the legend duration was 15 days for nimesulide, 8 days for acetylsalicylic acid, 7 days for morniflumate, 3 days for acetaminophen, and 5 days for all of the other drugs. In comparison with other non–niflumic acid NSAIDs, the adjusted RR for any mucocutaneous event among the children exposed to niflumic acid was 1.1 (95% CI: 0.9–1.4).

Excluding all the cases recorded during the 30-day carryover risk window after the end of the exposure time decreased the RR for niflumic acid to 0.8 (95% CI: 0.6–1.1) in comparison with other non–niflumic acid NSAIDs.

The exclusion of all the cases noted in the diary on the same date as the prescription (445) (eg, acetaminophen-induced exanthema) led to a RR of 0.9 (95% CI: 0.8–1.1) for niflumic acid in comparison with other non–niflumic acid NSAIDs.

TABLE 2. Patient Characteristics According to Prescribed Drug Class

Patient Characteristics	Niflumic Acid, %	Other NSAIDs, %	Acetaminophen, %	Other Analgesics, %	Total, *N*
Gender					
Female	47.5	48.1	48.2	48.1	38 256
Male	52.5	51.9	51.8	51.9	41 672
Age, y		*		*	
0–3	57.0	20.6	65.7	62.5	40 695
4–6	28.8	30.6	19.6	19.5	20 746
7–9	9.6	27.9	9.6	10.7	11 375
10–14	4.6	20.9	5.0	7.3	7116
Geographical area		*	*	*	
North	64.0	76.3	48.1	60.1	49 238
Center	23.0	14.9	20.2	23.4	16 446
South	13.0	8.9	31.7	16.5	14 248
Indications (mutually exclusive categories)		*	*	*	
Otitis media	9.9	7.4	9.9	4.5	7453
Upper respiratory tract infection	46.7	44.8	37.8	38.7	34 461
Gastrointestinal infection	0.5	.8	3.9	2.3	1354
Bronchitis/pneumonia	1.6	1.1	2.4	1.8	1386
Exanthematic disease	0.2	0.2	1.9	0.8	621
Other infectious diseases	5.4	7.0	15.2	9.3	7337
Symptoms of no clear origin	10.6	10.9	5.2	11.6	7199
Trauma (including articular and genital problems)	0.8	3.3	0.6	2.5	1163
History of allergy	0.2	0.2	0.2	0.3	265
Dermatological disease	0.1	0.1	0.1	0.2	109
General check-up	4.7	3.7	8.3	6.0	4418
Other	2.5	2.6	2.4	2.6	2233
Not coded/unknown	16.0	17.9	11.9	19.4	11 933
Use of NSAIDs during previous 30 d		*	*		
None	93.8	94.6	91.7	94.0	74 583
1 drug	5.9	5.1	7.6	5.6	5016
≥2 drugs	0.3	0.3	0.7	0.4	333
Concomitant drug use					
Antibiotics	35.5	34.3*	43.2*	32.3*	30 182
Penicillins	10.5	12.5*	14.7*	10.1	9930
Amoxicillin	6.5	5.5	10.4	7.2	6010
Amoxicillin + clavulanic acid	3.9	6.7	4.1	2.4	3753
Cephalosporins	16.9	14.0*	20.4*	14.7*	13 905
Cefuroxime	1.1	1.2	1.1	0.9	870
Cefaclor	5.9	4.4	8.8	5.3	5244
Cefixim	3.9	3.9	4.5	4.9	3348
Cefpodoxim	0.6	0.4	0.5	0.2	370
Ceftibuten	3.6	2.8	3.3	1.9	2579
Cefprozil	1.2	0.8	1.3	0.7	864
Sulfonamides	0.2	0.4*	0.7*	0.5*	338
Macrolides	8.6	8.4	7.9*	7.8	6635
Antimycotic agents	0.2	0.2	0.4*	0.2	237
Antimycobacterial agents	0.0	0.1	0.1	0.0	43
Antiviral agents	0.4	0.4	0.8*	0.2†	410
Total	30 121	19 401	24 052	3826	79 932

Comparison with niflumic acid category. *P* values are based on the χ^2 test: * $P < .01$; † $P < .05$.

DISCUSSION

The results of this retrospective cohort study in children showed very clear patterns of NSAID and nonopioid analgesic drug use; niflumic acid and acetaminophen were the most frequently prescribed drugs, predominantly among young children, whereas the prescription of other study drugs was less frequent and more oriented to older children. The incidence of mucocutaneous reactions during or after the use of any of the study drugs was inversely correlated with age for all the study drug classes. Furthermore, the incidence of severe or mild mucocutaneous reactions was virtually the same among the users of the different study drugs after adjusting for confounding factors, and in particular, niflumic acid was not associated with any increased risk in comparison with other NSAIDs or acetaminophen. This was true for the different age groups and various types of mucocutaneous reactions, was independent of the concomitant use of antibiotics, and was not sensitive to changes in our assumptions regarding exposure and outcomes.

The strength of this study lies in its design and data source. A cohort study can establish the temporal sequence between cause and effect, and the use of prescription data prospectively collected for purposes of routine patient care eliminated recall problems. Furthermore, the use of children exposed to other NSAIDs as the comparison group reduced potential confounding by indication. Given the large sample size and the wealth of information, we also were able to control for various classes of concomitant drug use, age, indication, and geographic region.

TABLE 3. Incidence Rates of Mucocutaneous Reactions Among Children With a Prescription of Any NSAID, Acetaminophen, or Nonopioid Analgesics According to Patient Characteristics and Concomitant Prescriptions of Other Drugs

Patient Characteristics	Severe Reactions				Mild Reactions			
	Cases	Incidence Rate Per 100 000 Person-Days	RR	95% CI of RR	Cases	Incidence Rate Per 1000 Person-Days	RR	95% CI of RR
Gender								
Female	18	9.3	0.8	0.4–1.5	670	3.5	0.9	0.8–1.0
Male	24	11.3	1 (reference)		781	3.8	1 (reference)	
Age, y								
0–3	28	13.5	1 (reference)		954	4.7	1 (reference)	
4–6	11	5.5	0.4	0.2–0.8	322	1.7	0.7	0.6–0.8
7–9	3	1.7	0.1	0.0–0.4	121	0.7	0.5	0.4–0.6
10–14	0	0.0	0		54	0.4	0.3	0.2–0.4
Geographical area								
North	31	12.5	1.8	0.7–4.2	821	3.3	0.7	0.6–0.8
Center	6	7.0	1 (reference)		401	4.9	1 (reference)	
South	5	6.9	1.0	0.3–3.2	229	3.2	0.7	0.5–0.8
Concomitant drug use*								
Any type of antibiotic	14	9.1	0.8	0.4–1.6	572	3.8	1.0	0.9–1.1
Penicillins	5	9.9	1.0	0.4–2.2	205	4.2	1.1	1.0–1.3
Cephalosporins	5	7.0	0.6	0.2–1.6	266	3.9	1.0	0.9–1.2
Sulfonamides	0	0.0	0		2	1.2	NA	
Macrolides	4	11.8	1.2	0.4–3.2	126	3.8	1.0	0.8–1.2
Antimycotic agents	0	0.0	0		20	17.2	5.5	3.5–8.7
Antimycobacterial agents	0	0.0	0		1	4.7	NA	
Antiviral agents	0	0.0	0		61	29.9	9.2	7.1–12.0
Indications								
Otitis media	2	5.3	1 (reference)		94	2.5	1 (reference)	
Upper respiratory tract infections	12	6.8	1.3	0.3–5.8	487	2.8	1.1	0.9–1.4
Gastrointestinal infections	1	14.5	2.8	0.3–30.4	19	2.8	1.1	0.7–1.8
Bronchitis/pneumonia	1	14.1	2.7	0.2–29.6	22	3.2	1.3	0.8–2
Other infectious disease	5	13.5	2.6	0.5–13.3	109	3.0	1.2	0.9–1.6
Exanthematic diseases	0	0	0		10	3.4	1.3	0.7–2.6
Trauma	0	0	0		10	1.7	0.7	0.4–1.3
Allergy	0	0	0		10	10.4	4.1	2.2–7.9
Dermatological disease	0	0	0		1	2.1	0.9	0.1–6.1
General check-up	1	4.5	0.9	0.1–9.4	49	2.2	0.9	0.6–1.2
Symptoms without clear origin	3	8.3	1.6	0.3–9.4	80	2.2	0.9	0.7–1.2
Other	1	8.8	1.7	0.2–18.4	21	2.1	0.8	0.5–1.3
Not coded/unknown	16	26.4	5	1.2–21.8	539	8.8	3.5	2.8–4.3
Total	42	10.3			1451	3.7		

* Reference is the group of nonusers of the specific drug.

Our study also has some limitations concerning the ascertainment and misclassification of exposure and outcome, mainly because of the use of an automated data source. The most serious is the lack of information about the over-the-counter (OTC) use of acetaminophen and NSAIDs. Although acetaminophen prescriptions are recorded in the database, they probably do not fully capture its global use; the children using OTC acetaminophen were not included because our cohort was created on the basis of a prescription. However, the incidence of acetaminophen-associated mucocutaneous reactions would be different from that estimated by us only if the children using OTC acetaminophen have a different likelihood of developing such reactions. Some of our children with NSAID prescriptions may have concurrently used OTC acetaminophen, but this potential use is unlikely to be differential in relation to niflumic acid and other NSAIDs and, in any case, would only affect the observed incidence for combinations and not that relating to the use of acetaminophen alone. We did not use acetaminophen as the reference group to avoid possible differential misclassification biases caused by the lack of information concerning its OTC use.

Another possible cause of exposure misclassification is the 5-day fixed exposure period applied to all the study drugs, which was chosen because more than half of the study-drug prescriptions could only be identified in the diary section of the electronic medical records, which contained no information concerning the prescribed duration. However, the sensitivity analysis using drug-specific legend durations based on the prescribed quantity showed that the fixed exposure duration cannot have hidden a potential association between niflumic acid and mucocutaneous reactions.

Outcome misclassifications caused by nonregistration in the FP records may have occurred for mild outcomes, but if this happened, it is likely to be nondifferential because the data refer to a period preceding the sending of the "Dear Doctor" letter. To rule out any potential outcome misclassification caused by the inclusion of false-positive cases, we conducted a sensitivity analysis excluding all the cases with an indication of exanthematic, dermatological, or other infectious diseases and did not find any changes in the RRs. Furthermore, the fact that antibiotics were associated with the reactions they are known to cause (erythema/rash and urticaria)

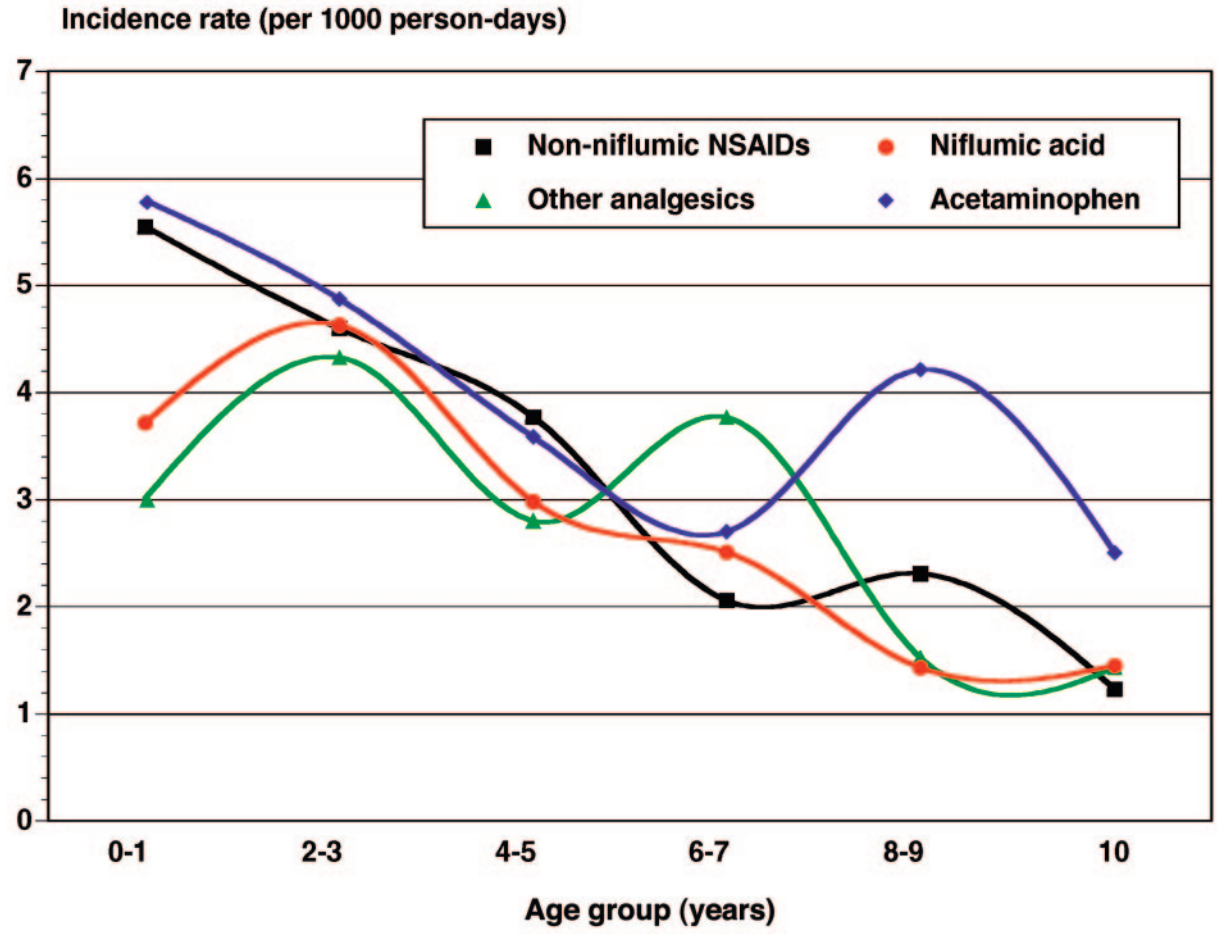

Fig 2. Incidence of mild or severe mucocutaneous reactions during the use of NSAIDs, acetaminophen, or nonopioid analgesics according to age in a cohort of 45 351 Italian children: 1998–2001.

TABLE 4. Incidence Rates and RRs of Mucocutaneous Reactions After the Use of NSAIDs, Acetaminophen, and Other Nonopioid Analgesics

	Cases	Person-Days	Incidence Rate*	Crude RR	Adjusted RR†	95% CI
Severe reactions						
Non–niflumic acid NSAIDs	10	98 165	10.2	1 (reference)	1 (reference)	
Niflumic acid	13	153 102	8.5	0.8	0.5	0.23–1.27
Acetaminophen	16	122 824	13.0	1.3	0.8	0.35–1.86
Other analgesics$	3	19 448	15.4	1.5	0.9	0.27–3.20
Combinations with niflumic acid	0	6113				
Combinations without niflumic acid	0	6907				
Total	42	406 559	10.3			
Mild reactions						
Non–niflumic acid NSAIDs	266	96 695	2.8	1 (reference)	1 (reference)	
Niflumic acid	510	150 205	3.4	1.2	0.9	0.79–1.11
Acetaminophen	551	119 525	4.6	1.7	1.1	0.95–1.35
Other analgesics‡	57	19 065	3.0	1.1	0.8	0.60–1.14
Combinations with niflumic acid	40	6661	6.0	2.2	1.2	0.87–1.77
Combinations without niflumic acid	27	5901	0.3	0.1	1.3	0.85–2.03
Total	1451	398 052	3.7			

* The incidence rate shown for severe reactions is per 100 000 person-days; the rate shown for mild reactions is per 1000 person-days.
† The RRs for severe reactions were adjusted for age; the RRs for mild reactions were adjusted for age, indication, region, and concomitant use of antimycotic and antiviral agents.
‡ Includes N02BB (pyrazolinone derivatives), N02BA (acetylsalicylic acid derivatives).

adds to the internal validity of the study. The events classified as severe may not all have been so in the sense of the usual definition as life-threatening or leading to hospitalization. However, when the severe cases were limited to those who were hospitalized, the conclusion of no association did not change. All the severe mucocutaneous events identified in the hospitalization files provided by the local health authority were included in the FP records, and thus it is highly likely that the case ascertainment of severe events was complete.

Our findings conflict with those of the hospital-

based case-control study conducted in Naples, Italy, by Menniti-Ippolito et al,[1] whose choice of exposure reference group (children not using any drugs) may have introduced confounding by indication. Children who do not use any drugs are not comparable with those receiving (multiple) drug treatment, because they are very likely to have a milder prognosis, less severe disease, and the absence of fever. Our study also showed that age is an important confounder, because a young age was closely associated with both the use of niflumic acid and the occurrence of mucocutaneous reactions. The results of the Naples study were not adjusted for age (10 of the 15 cases of mucocutaneous reaction after exposure to niflumic acid occurred in children who were <5 years old; the age distribution of the control group was not shown). In addition, the Naples study may not be exempt from a "protopathic bias," which could partly explain the high RR for niflumic acid: an association between drug use and an adverse reaction erroneously appears when the event's prodromal symptoms are treated with the drug studied as a potential risk factor.

To the best of our knowledge, this is the first population-based study of the incidence of mucocutaneous reactions in relation to treatment with NSAIDs or analgesics among children. We did not find any increase in the risk of severe or mild mucocutaneous reactions with niflumic acid in comparison with other NSAIDs or acetaminophen.

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