SHORT REPORT

Niflumic acid and cutaneous reactions in children

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Abstract

In a case control study of adverse drug reactions in children, the odds ratio of developing a serious mucocutaneous event among users of niflumic acid, adjusted for concomitant use of all other drugs, was 4.9 (95% CI 1.9 to 12.8). Given the availability of safer analgesics and antipyretics, there is no indication, in our opinion, that requires the prescription of substances which bear an increased risk.

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Keywords: adverse drug reactions; niflumic acid; cutaneous reactions; pharmacoepidemiology

Niflumic acid and morniflumate (its betamorpholinoethyl ester; in the following also referred to as niflumic acid), are non-steroidal anti-inflammatory drugs (NSAIDs), widely prescribed in children in Italy. The drug is also marketed for use in adults and children in France, Spain, and Portugal, and for adults only in Belgium, Luxemburg, Switzerland, Germany, and Greece. During 1999, of the 4 200 000 packs sold to the general population in Italy, almost 2 400 000 were paediatric suppositories, and 900 000 packs were oral granules, which are recommended for use in children according to the leaflet (data provided by the Italian Ministry of Health on the basis of IMS (International Marketing Statistics) data).

NSAIDs may cause dermatological reactions, the most common being rash/urticaria, which are usually not serious and resolve rapidly. There have been two reports of an

association of Lyell's syndrome with use of niflumic acid.^{1 2}

In November 1999, an active surveillance of adverse drug reactions was set up in a large paediatric hospital in Naples (the Santobono hospital) in which there are around 20 000 admissions and 45 000 visits to the emergency department per year. Several months after the beginning of the study, our attention was drawn to the fact that some children were hospitalised for serious mucocutaneous conditions and had used niflumic acid. In order to describe the characteristics of these patients and to quantify the potential risk associated with use of niflumic acid, we focused our analysis on mucocutaneous events occurring during the first year of surveillance.

Methods

The hospital surveillance was organised as a case control study. We enrolled all children admitted through the emergency department, regardless of drug exposure, for the following four conditions: endoscopically confirmed gastro-duodenal lesions; neurological disorders (convulsions are included only if not associated with fever); non-infectious mucocutaneous diseases and vasculitis; and thrombocytopenia (less than 100 000 platelets). Children admitted for a suspected adverse drug reaction were also followed up, but not included in the case control study if the admission was for a different disorder, for example, anaphylaxis. Children with a concomitant diagnosis of cancer, immunodeficiency, or chronic renal failure were excluded.

For each patient, the prescription and vaccination history preceding admission (three

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Table 1 Description of patients exposed to niflumic acid or morniflumate

Adverse reaction	Age	Gender	Other drugs	Indications
Stevens–Johnson	10 mth	Female	—	Pharyngitis
Exanthematous eruption	2 y	Male	Paracetamol	Cough
Vasculitis	2 y	Male	Beclametasone, bactolysatum	Pharyngitis
Vasculitis	3 y	Female	Amoxicillin, flurbiprofen, rokitamycin, fusidic acid	Pharyngitis
Urticaria	3 y	Male	Clarithromycin, betamethasone, cefaclor, paracetamol	Otitis
Vasculitis	3 y	Female	Sobrerolum, salbutamol	Common cold
Schönlein–Henoch	4 y	Male	Ceftibuten, ambroxol	Red throat
Schönlein–Henoch	4 y	Female	Paracetamol, mebendazole	Fever, parasitosis
Urticaria	4 y	Female	Paracetamol, cefixime, vaccinum subtilicum	Diarrhoea, fever, pharyngitis
Vasculitis	4 y	Male	—	Tonsillitis
Vasculitis, orchitis, Schönlein–Henoch	5 y	Male	Cefaclor, paracetamol, carbocysteine	Cough
Urticaria	6 y	Female	Clarithromycin, vitamins	Pharyngitis
Vasculitis	7 y	Male	Phenazone + procaine, paracetamol, amoxicillin + clavulanate, clarithromycin	Otitis
Vasculitis	10 y	Female	Amoxicilline + clavulanate, acetylsalicylic acid + ascorbic acid, erythromycin, benzathine benzylpenicillin	Tonsillitis
Vasculitis	10 y	Male	Cephalosporins, amoxicillin	Pharyngitis, tonsillitis

Table 2 Odds ratios (OR) with 95% confidence intervals (CI) of developing mucocutaneous reactions among users of different drugs

Drugs	Cases (n = 79)	Controls (n = 162)	Crude ORs (95% CI)	Adjusted* ORs (95% CI)
Niflumic acid	15	7	8.2 (2.7 to 25.1)	4.9 (1.9 to 12.8)
Amoxicillin + clavulanate	10	6	6.4 (1.9 to 21.5)	3.6 (1.2 to 10.4)
Any antibiotic	39	57	2.6 (1.2 to 5.6)	1.6 (0.9 to 2.8)
Paracetamol	18	29	2.4 (0.99 to 5.7)	1.2 (0.6 to 2.4)
Non-users	12	46	1	1

*Odds ratios were adjusted for concomitant use of any other drug.

weeks for drugs and six weeks for vaccinations) was obtained by interviewing parents, using a structured questionnaire. Data on age, gender, body mass index, education of parents, number of members in household, chronic diseases, allergies, and characteristics of the prescription (for example, indication), were also collected.

For each condition, all patients enrolled for the three other conditions were considered as controls. In the analysis, children admitted for mucocutaneous disorders were compared to those hospitalised for the three remaining conditions. All children younger than 1 month were excluded from analysis.

Results

From November 1999 to October 2000, 241 children were admitted with mucocutaneous diseases (n = 79), gastrointestinal lesions (n = 37), neurological disorders (n = 78), and thrombocytopenia (n = 47). Among the 79 children hospitalised with mucocutaneous diseases, 15 (19%) had used either niflumic acid or morniflumate. In particular, we observed one case of Stevens–Johnson syndrome, three of Schönlein–Henoch purpura, seven of vasculitis, three of urticaria, and one of exanthematous eruption (table 1). Seven users of niflumic acid (4% of 162 children) were observed in the control group. In addition to niflumic acid, we also analysed those substances with at least 10 exposed cases (amoxicillin plus clavulanate, and paracetamol). Antibiotics, the drugs most frequently used in the study population, were also analysed as a class.

The odds ratio of developing a mucocutaneous event among users of niflumic acid,

adjusted for concomitant use of all other drugs, was 4.9 (95% confidence interval (CI) 1.9 to 12.8). The corresponding odds ratio for amoxicillin plus clavulanate was 3.6 (95% CI 1.2 to 10.4) and for paracetamol was 1.2 (95% CI 0.6 to 2.4). Users of any antibiotic presented an odds ratio of 1.6 (95% CI: 0.9 to 2.8) (see table 2). Because of power considerations, we were not able to control for other potential confounding factors.

Conclusions

Given the magnitude of the odds ratios observed for users of niflumic acid and of antibiotics (in particular, amoxicillin plus clavulanate), it is unlikely that biases in selecting the study population and in acquiring information may explain the results. It is well known that antibiotics may cause mucocutaneous reactions. However, given the efficacy of antibiotics, the only question in the assessment of the risk/benefit profile is related to the appropriateness of prescriptions.

The case of niflumic acid is quite different. Given the availability of safer analgesics and antipyretics (for example, paracetamol) in children, there is no indication that requires the prescription of substances which bear an increased risk of severe reactions. In our population, 19% of children who developed mucocutaneous disorders had used niflumic acid. On the basis of the observed odds ratios, we estimate that more than 80% of these hospitalisations (and around 15% of all mucocutaneous hospitalisations) could have been prevented. Though our findings may need additional corroborating evidence, it would be wise to adopt a precautionary attitude and to restrict the use of niflumic acid (and morniflumate) in children.

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- 2 Raymond F, Paillat A, Gambert C, Garnier P. Lyell syndrome following administration of erythromycin-sulfafurazole and morniflumate. *Arch Pediatr* 1995;2:494–5.