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Severe necrotizing soft-tissue infections and nonsteroidal anti-inflammatory drugs

C. Souyri,*† P. Olivier,* S. Grolleau,‡ M. Lapeyre-Mestre‡ and the French Network of Pharmacovigilance Centres

*Department of Clinical Pharmacology, Pharmacovigilance Regional Centre, Toulouse University Hospital, Toulouse France; †Department of Hospital Pharmacy, Toulouse, University Hospital, Toulouse France; and ‡EA3696, Unit of Pharmacopidemiology, Department of Clinical Pharmacology, University Paul Sabatier, Toulouse, France

Summary

Background. Severe necrotizing soft-tissue infection (NSTI) is a rare but potentially life-threatening condition if not recognized and treated early. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been implicated as a contributing factor, but their role remains debated.

Aims. The aim of our study was to investigate the potential relationship between cases of NSTI recorded in the French Pharmacovigilance system and exposure to NSAIDs.

Methods. Cases of NSTI and randomly selected matched noncase controls (without skin disease) were identified in the database of the Spontaneous Reporting System in France for the period 2000–2004. Exposure to NSAIDs and other factors were investigated using conditional logistic regression.

Results. We found 38 cases of NSTI in 2000–04: 12 infants (0–23 months), 16 children (2–15 years) and 10 adults (>15 years), and we selected 228 controls. The median age of the sample was 4 years. Of the 38 cases, 25 were exposed to ibuprofen and 24 presented with varicella. The adjusted odds ratio for exposure to NSAIDs was 31.38 (95% CI 6.40–153.84), and 17.55 (95% CI 3.47–88.65) for viral infection. Other predisposing factors (diabetes, immunosuppression, injecting drugs) were not found to be associated, although this may have been due to the very small number of cases of NSTI/necrotizing fasciitis in adults reported in the database.

Conclusion. Despite the limitations related to a spontaneous reporting system, this study indicates a strong association between NSAID use and NSTI. Although it was not possible to conclude if NSAIDs increase the risk of necrotizing complications in all patients, their use may mask the symptoms and delay diagnosis.

Correspondence: Dr M. Lapeyre-Mestre, Unit of Pharmacoepidemiology EA3696, Department of Clinical Pharmacology, Faculté de Medecine, 37 Allees Jules Guesde, 31000 Toulouse, France.
E-mail: lapeyre@cict.fr

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Introduction

Bacterial infections of the skin and its structures are common clinical problems. Such infections are sometimes deeper and more severe, with bacterial multiplication within the dermis and hypodermis, leading to vascular thrombosis and eventually to tissue necrosis. Necrotizing fasciitis (NF) is defined by the progression of necrosis over the superficial fascia.[1] Such cases of severe necrotizing soft-tissue infections (NSTI) are rare but potentially life-threatening if not recognized and treated early.[2] The organisms most closely linked to NSTI are group A β-haemolytic streptococci, although

the disease may also be caused by other bacteria or different streptococcal serotypes.[3]

Aggressive surgical debridement, intravenous broad-spectrum empirical antibiotics, fluid and electrolyte management, and analgesia are mainstays of treatment, but the mortality rate remains high (30–60%). Underlying debilitating diseases are predisposing factors, but previously well patients can also be affected.[2] The use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been implicated as a contributing factor.[4–6] The hypothesis that NSAIDs might increase the risk of necrotizing fasciitis in children was suggested during the 1990s,[7,8] especially in association with varicella infection. In July 2004, the French Medicine Agency (AFSSAPS) sent a letter to general practitioners, advising against the use of NSAIDs in children with varicella because of the risks of serious skin infections.[9]

The aim of our study was to investigate the potential association between NSTI and NSAIDs, whatever the context (type of NSAID, age, varicella or other viral infection), in the French Pharmacovigilance database.

Materials and methods

Source

The French Pharmacovigilance Database contains all adverse drug reactions (ADR) reported to the French Regional Pharmacovigilance Centres by health care professionals. In France, spontaneous reporting for all prescribers (medical doctors, dentists and midwives) and pharmacists has been compulsory since 1995 for any ADR defined as serious and/or unexpected.[10] For each report, information about the ADR, patient (age, gender, medical history) and treatment (suspected and concomitantly used drugs) are recorded. There is a free text section in the form, in which the centre collecting the data can add remarks. ADR are coded according to the World Health Organization Adverse Reaction Terminology (WHO-ART).[10] For this study, all serious ADR (i.e. life-threatening, leading to disability or death, or requiring hospitalization) recorded in the database between January 2000 and December 2004 were used.

Case–control design

The study method has been described previously and corresponds to a case-control design.[11] Cases are represented by all reports corresponding to the event of interest (drug-related NSTI). Non-case controls are the reports corresponding to all other drug-related events. The principle is to compare drug exposure (i.e. all drugs taken before the drug-related event as mentioned in the spontaneous report) of cases and controls.

Selection of cases and controls

We searched all potential cases of NSTI in the pharmacovigilance database with a list of WHO-ART codes describing NF, but also codes describing other skin damages with inflammation and infection, or systemic manifestations potentially related to NSTI (Table 1). The list of codes was large, to allow sensitive searching, then, after careful examination of the medical records, we only included patients with ADR corresponding to a probable or definite NSTI. Criteria of diagnosis were the presence of signs of necrotizing infections (e.g. skin necrosis, rapid progression of the lesion, systemic toxicity, haemodynamic instability), or confirmed diagnosis by surgical debridement.

From the other non-NSTI serious reports collected during the same period, we randomly selected six controls for each case, matched on age, gender and year of reporting (±1 year). In order to minimize misclassification bias, we did not include controls with an ADR involving the skin.

Table 1 List of WHO-ART codes used to search potential cases of necrotizing soft-tissue infections in the French Pharmacovigilance database

WHO-ART code	Reaction
13 003	Necrotizing dermatitis
37 006	Cutaneous infection
32 005	Pyodermitis
1 339 001	Gangrenous pyodermatitis
1 746 001	Necrotizing fasciitis
1 707 001	Fasciitis
1 355 001	Folliculitis
16 001	Extended furuncle
85 005	Cutaneous vascularitis
1 210 003	Muscular necrosis
1 516 001	Varicella
738 001	Bacterial infection
744 004	Staphylococcal septicaemia
499 003	Shock
748 001	Myositis
469 001	Cerebral thrombophlebitis
887 003	Cutaneous abscess
941 001	Sepsis
1 226 001	Increased susceptibility to infections
737 001	Cutaneous infection
453 001	Peripheral gangrene
60 001	Cutaneous necrosis
1 372 001	Cellulitis
911 001	Peripheral gangrene

WHO-ART, World Health Organization Adverse Reaction Terminology.

Exposure definition

Exposure in cases and controls was defined by the presence in the report of at least one NSAID taken before the reaction. Aspirin was not included in the group of NSAIDs, as it was used mostly as an antiplatelet agent. The NSAID was taken into account if its causality assessment was estimated as at least 'possible'.[10] The other drugs were classified according to the Anatomical Therapeutic Chemical Classification (ATC).

Sample size calculation

Our search hypothesis was based on an NSTI risk with NSAID use, similar to that observed in previous studies focusing on complicated primary varicella and ibuprofen.[12–14] This level of risk estimated by odds ratios (OR) from case–control studies varies between 3.9 in the Lesko and Choo studies[12,14] to 11.5 in the Zerr study.[13] The expected prevalence of exposure to NSAIDs in the control group was 6% according to data obtained in the French population.[15] Thus, we estimated that we had to include six controls for each case for an expected OR ≥ 4.5 with a risk (α) of 5% and a power of 80%.

Statistical analysis

We used the χ^2 test to compare proportions and Wilcoxon's rank sum test to compare continuous variables. The exposure OR was used as the measure of association between drug use and the risk of NSTI. We compared the exposure to the main therapeutic classes of drugs and to NSAIDs and corticosteroids between cases and controls. We also took into account drug use as a proxy of any medical condition known as a risk factor for necrotizing infection [e.g. drugs used in the treatment of human immunodeficiency virus (HIV), diabetes or cancer]. We defined a category of drug exposure corresponding to corticosteroids, anti-HIV drugs and/or immunosuppressant and anticancer drugs as 'immunosuppression'.

We calculated univariate and multivariate ORs with 95% confidence interval (CI) using conditional logistic regression. In the multivariate analysis, the conditional logistic regression included as independent variables matching factors (age, gender, year of reporting to the pharmacovigilance system), NSAIDs, aspirin, paracetamol, and immunosuppression. Analyses were performed with SPSS software (version 11.5 for Windows; SPSS Inc., Chicago, IL, USA) and SAS software for conditional logistic regression (version 9.3, Proc PHREG; SAS Institute, Cary, NC, USA).

Results

Of the 41 247 serious cases recorded in the French Pharmacovigilance database during the study period, 1951 concerned cases of serious skin ADR. We identified 38 cases of NSTI [12 infants (0–23 months), 16 children (2–15 years) and 10 adults (>15 years)], and we selected 228 matched controls (Table 2). The WHO-ART codes used to record these adverse reactions were not always accurate, with only 13 cases having a specific WHO-ART code of NSTI (Table 2). Four cases were reported in 2000, 5 in 2001, 16 in 2002, 8 in 2003 and 5 in 2004; 55% of cases were male, median age was 4 years, and the third quartile was 12 years (range 4 months to 79 years).

The seriousness of the reaction varied from varicella with necrotizing skin lesions to NSTI with toxic shock syndrome; there were 12 cases of the latter, more severe condition. Infection was not restricted to any particular body site: 7 cases occurred on the perineum, 5 on the face, 11 on the chest, 6 on the upper limbs, 6 on the lower limbs and 8 over the total body.

There were positive microbiological results in 66% of cases, and positive blood results in 25% of cases. Group A streptococci (GAS) were mainly found (47%) followed by staphylococci (23%) and Gram-negative strains (*Pseudomonas aeruginosa*, *Proteus*, *Colibacillus*).

Of the 28 children, 26 had varicella and 2 had other viral infections, and of these 24 patients, 22 had taken NSAIDs (18 ibuprofen, 2 niflumic acid and 2 ibuprofen and niflumic acid concomitantly). The mean ± SD delay of occurrence of the event after NSAID use was 4.2 ± 5.6 days (median 3, third quartile 4). Of the two remaining paediatric patients, the clinical context was trauma in a 7-year-old boy and was unknown in a 3-month-old boy. A surgical debridement was performed for four patients, and a skin graft was necessary in two. The mortality rate was 10.7% in the child group.

The clinical context in the adult group was injury in three patients, and iatrogenic procedures [vaccine, abdominal infusion of leuproreline (a luteinizing hormone-releasing hormone agonist for the treatment of prostate cancer), anal anastomosis] in a further three patients. None of the adults had a known viral infection and six of them had been exposed to NSAIDs (three ibuprofen, two ketoprofen, one rofecoxib). The mean ± SD delay of occurrence after NSAID use in adults was 9 ± 11.9 days (median 3, third quartile 7). The mortality rate was 50%.

Table 2 Characteristics of cases and non-case controls according to gender, age, type of adverse drug reaction (WHO-ART classification) and drug exposure (ATC classification)

Variables	Cases (n = 38)		Controls (n = 228)
Male gender	21 (55.3)		126 (55.3)
Age (mean ± SD)	18.46 ± 26.87		18.55 ± 26.58
Classes of age			
Infants	12 (316)		72 (31.6)
Children	16 (42.1)		96 (42.1)
Adults	10 (26.3)		60 (26.3)
Viral infection	26 (68.4)		23 (10.1)
Varicella	24 (63.1)		0 (0)
WHO-ART codes		System/organ class	
Cellulitis	11 (28.9)	Musculoskeletal system	8 (3.5)
Necrotizing fasciitis	11 (28.9)	Nervous system	38 (16.7)
Skin necrosis	7 (18.4)	Gastrointestinal system	15 (6.6)
Skin infection	2 (5.4)	Liver and bile ducts	13 (5.7)
Septicaemia	2 (5.4)	Metabolism	7 (3.1)
Necrotizing fasciitis and cellulitis	1 (2.6)	Cardiovascular system	13 (5.7)
Necrotizing fasciitis, cellulitis and pyodermitis	1 (2.6)	Heart and valves	14 (6.1)
Dermitis with pyogenes	1 (2.6)	Respiratory system	12 (5.3)
Pyodermitis	1 (2.6)	Red and white blood cells	7 (3.1)
Complicated varicella	1 (2.6)	Blood and coagulation	6 (2.6)
		Health status	46 (20.2)
		Host defences	4 (1.8)
ATC classes			
Alimentary tract and metabolism	2 (5.3)		29 (12.7)
Blood and blood forming organs	1 (2.6)		28 (12.3)
Cardiovascular system	0 (0)*		25 (11.0)*
Dermatologicals	8 (21.1)***		1 (0.4)***
Systemic hormonal preparations	2 (5.3)		22 (9.6)
Anti-infectives for systemic use	10 (26.3)		93 (40.8)
Antineoplastic and immunomodulating agents	5 (13.2)		44 (19.3)
Musculoskeletal system	31 (81.6)**		28 (12.3)**
Nervous system	14 (36.8)		73 (32.0)
Respiratory system	10 (26.3)**		21 (9.2)**
Various	0 (0)		3 (1.3)

ATC, Anatomical Therapeutic Chemical; WHO-ART, World Health Organization Adverse Reaction Terminology. Data are n (%) unless otherwise indicated; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Association with drug exposure

The analysis of drug exposure between cases and controls found a higher frequency of dermatological drugs (antiseptic and antipruritus drugs) and drugs for musculoskeletal disorders in cases (Table 2). We also found a significant association with NSAIDs (OR = 67.46; 95% CI 16.00–284.20) and paracetamol (OR = 5.69; 95% CI 2.34–13.80). Other drugs (e.g. corticosteroids, immunosuppressants) were not associated (Table 3). We did not identify any case with other predisposing factors (diabetes, injecting drugs). The OR for viral infections was 36.49 (95% CI 10.89–122.30). The final model of multivariate conditional logistic regression retained only significant independent variables, i.e. NSAIDs (OR = 31.38; 95% CI 6.40–153.84) and viral infection (OR = 17.55; 95% CI 3.47–88.65) (Table 3).

Discussion

We found a strong association between NSAIDs and severe necrotizing cutaneous infections, particularly in children with varicella. However, the number of cases was very low, comprising only 1.9% of all serious skin reactions reported during the same period.

NSAIDs and paracetamol were found to be associated with NSTI. In the multivariate analysis, only NSAIDs and viral infections remained associated. The OR was lower, suggesting a confounding effect of the viral infection. Some investigators have hypothesized that NSAIDs increase the risk of necrotizing fascitis,

Table 3 Crude and adjusted odds ratio for specific drug exposure in cases and non-case controls estimated from the conditional logistic regression

	Cases (n = 38) n (%)	Controls (n = 228) n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Male gender	21 (55.3)	126 (55.3)	1.00 (0.48–2.11)	–
Age	–	–	1.00 (0.98–1.01)	–
Viral infection	26 (68.4)	23 (10.1)	36.49 (10.89–122.3)	17.55 (3.47–88.65)
NSAIDs	30 (78.9)	16 (7.0)	67.46 (16.00–284.20)	31.38 (6.40–153.84)
Paracetamol	12 (31.6)	18 (7.9)	5.69 (2.34–13.80)	0.93 (0.28–3.11)
Vaccines	2 (5.2)	35 (15.4)	0.31 (0.03–1.29)	–
Aspirin	1 (2.6)	13 (5.7)	0.45 (0.01–3.16)	–
Immunoglobulins	0 (0.0)	8 (3.5)	0.00 (0.00–4.09)	–
Corticosteroids*	4 (5.3)	22 (9.6)	1.16 (0.32–3.40)	–
Antiretroviral drugs	0 (0.0)	3 (1.3)	0.00 (0.00–13.82)	–
Immunosuppression**	7 (18.4)	57 (25.0)	0.67 (0.28–1.62)	–

ATC, Anatomical Therapeutic Chemical; NSAIDs, nonsteroidal anti-inflammatory drugs; WHO-ART, World Health Organization Adverse Reaction Terminology. *Corticosteroids from ATC class 'Dermatologicals' 'Systemic hormonal preparations' and 'Respiratory system'; **immunosuppression: drugs from ATC class 'Antineoplastic and immunomodulating agents' antiretroviral drugs and corticosteroids as defined above.

particularly among children with varicella.[5,16] Zerr *et al.* found that NSAID use was significantly more common among patients with varicella or NF than among controls[13] but in more than three-quarters of the cases, the NSAID use occurred after the onset of symptoms of secondary infection. This suggests that an 'indication bias' may be due to NSAIDs being given as a response to infection in patients with severe disease rather than being a cause of the severity of the illness. This indication bias may also be important in our study. We were not able to investigate the delay between onset of varicella when present and onset of the symptoms of the secondary infection, but we observed a delay of 1–5 days after the initiation of NSAID use, compatible with the findings of Zerr *et al.*

In an animal model of necrotizing infection, treatment with diclofenac significantly limited NSTI spread.[17] However, a specific inverse relationship between the extent of inflammation and bacterial density in NSTI lesions was observed after inoculation in the groups exposed to diclofenac. This observation suggests that the greater severity of NSTI in humans treated with an NSAID may be due to the delay in treatment induced by the misleading clinical effects of the NSAID and not to inhibition of antibacterial defence.[17] Thus it is important to reinforce warnings about the use of NSAIDs in children with varicella.

Several host factors were found to be associated with an increased risk of invasive GAS disease in adults.[18] Acquired immune suppression increases the risk for invasive GAS disease in patients with HIV infection. The association with injecting drug use may be due to the direct injection of group A streptococci from the skin into the blood.[19] In older adults, diabetes mellitus, cardiac disease, cancer, and corticosteroid use are associated with invasive GAS infection, suggesting a role for immune dysfunction.[18–20] Unfortunately, we did not find any association with these factors in the French database. There may be several explanations. Firstly, very few adult patients were identified in the database with an ADR related to a severe necrotizing skin infection. When we analysed the risk associated with exposure to immunosuppressant drugs or with drugs used for HIV infection, we did not find any association. Moreover, we did not identify any diabetic patients or people addicted to intravenous drugs in our case group. It is possible that patients with diabetes and complicated necrotizing skin infections were not considered to have an ADR. Similarly, patients with drug addiction presenting infections after injecting buprenorphine or other narcotic drugs were recorded in the French database with a code of 'dependence' or 'drug abuse', rather than a skin reaction.

Varicella infection is a well-documented risk factor in the development of invasive GAS disease among children[4–6] and adults.[18] In our study, we found a strong association between NSTI and viral infections, and the we also observed the presence of varicella in most of the patients. This finding constitutes another limitation in investigating the individual role of NSAIDs, as varicella could itself be complicated by necrotizing infection with or without use of NSAIDs.

In the Boston University Fever Study, comparing the safety of ibuprofen and paracetamol in febrile children, no significant difference was observed for the risk of hospital admission or the risk of renal function impairment.[21]

Moreover, admissions for asthma or cellulitis and physician visits for abdominal pain or dyspepsia were similar for the two drugs. In the study of Lesko *et al.*, there was no association with the use of ibuprofen or paracetamol alone, but the use of both agents was significantly associated with streptococcal infection.[14] Neither agent was associated with an increased risk of necrotizing soft-tissue infections.

Concerning the limits of the database, a notoriety bias in the reporting of cases of complicated varicella with NSAIDs in children could be suspected, but this is unlikely, given that the number of cases remained stable during the study period and did not increase in 2004. Moreover, some of the true cases of NSTI were not reported with a code of NSTI. On the other hand, by excluding all patients with a cutaneous reaction from the control group, the risk of exposure to NSAIDs may be overestimated. We applied this exclusion criterion to avoid misclassification of cases, because it was sometimes difficult with several reports to exclude a necrotizing complication of a skin ADR. However, despite the exclusion of these reports, the characteristics of the controls were similar to those described in other pharmacovigilance descriptive studies.[9,22] The prevalence of NSAID or paracetamol exposure found in our control group is also very close than that observed in the French general population, suggesting that this bias was not particularly important.[14,23]

Conclusion

Despite the limits related to a spontaneous reporting system, this study indicates a strong association between NSAID use and NSTI. Most of cases identified in the French pharmacovigilance database concerned children aged <15 years with varicella treated by ibuprofen, suggesting an indication bias. The greater severity of NSTI in children treated with NSAIDs may be due to the masking effects of drugs and to the therapeutic delay rather than to the alteration of bacterial defences.

Concerning the risk of NSTI with NSAIDs in adults, we found very few cases in the pharmacovigilance database. Several cases have been reported in the literature, but the data are not sufficient to give rational guidelines about the use of these drugs in the context of soft-tissue infections in adults.

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