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The Risk of Worsening Infections under Non-steroidal Anti-inflammatory: A French Observational Study

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Abstract

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used to relieve pain, fever or inflammation; and information on secondary infectious risk is unclear. The aim of our study is to describe the cases of worsening infections under NSAIDs to question the risk.

Methods: To investigate this potential risk, we performed a prospective, observational and single-center study.

Results: In total, 28 cases of worsening infection after exposure to NSAIDs were included in the study. The most frequently involved NSAID was ibuprofen (64%) and the NSAIDs were primarily used as painkiller (47%) and against fever (35%). The most frequent sites of infection were cutaneous (32%) and pulmonary (22%). We noted that the infection was resolved for 86% of our patients. The most serious cases required admission to the intensive care unit (14%) and one patient died.

Conclusions: The wide diversity of cases observed in our small group of patients suggests that all types of infection may be concerned. Other analgesic or antipyretic drugs should be preferred over NSAIDs when there is suspected infection. Information has to be more transparent regarding to the potential risk of serious worsening of infection after exposure to NSAIDs.

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used as painkillers, and to treat fever and inflammation. Several NSAIDs are available over the counter for self-medication, and are sometimes used inappropriately. And even if the French National Agency for Medicines and Health Products Safety (ANSM) recently sounded the alarm on the use of NSAIDs in a context of infection [1], it has never been convincingly demonstrated that taking these products can cause an ongoing infection to worsen, and a new warning about the risk of using these products in an infectious situation is always an interesting signal in terms of public health. Information on the packaging of NSAIDs is vague and rather reassuring regarding secondary infectious risks. Besides, available data in this regard are conflicting, with studies focusing on only one type of infection, or a specific patient population. The largest body of evidence exists in the context of cutaneous infections and complications occurring in children [1].

In this context, we decided to perform a prospective and observational study of worsening infection following exposure to NSAIDs in two specialized wards of a university hospital over a period of one year. The objective was to collect the cases occurring in this setting, to describe the types of patients affected, the drugs used, the circumstances of the occurrence, as well as the type of infection and deterioration observed.

Methods

We performed a prospective, observational, single-center study. All patients hospitalized between February 2014 and February 2015 in an Infectious Diseases ward (72 beds) or a Pediatric Unit (48 beds) with a history of recent administration of NSAIDs and presenting bacterial infection were included. The primary endpoint was worsening of infection, as assessed according to the course of the infection compared to the patient's initial status. This study was conducted in accordance with the approved guidelines of the institutional review board of Reims University Hospital and in accordance with the 1964 Declaration of Helsinki. Each patient and parent/legal guardian, for patients under 18, provided oral informed consent before conducting the experiments in accordance with relevant guidelines and regulations. Worsening infection was judged by the clinicians who follow patients on the criteria of: onset of complications of infection, dissemination of infection, abscess, unexpectedly serious signs, and prolonged need for treatment, severe sepsis or septic shock. The exposure to NSAIDs had to have occurred prior to the initial suspicion of infection, and worsening had to have occurred after the ingestion of NSAIDs without more evident causes. If there was any doubt about the chronology of the exposure to NSAIDs, occurrence of the primary endpoint, or strong confounders for the worsening, the patient was excluded.

For all patients, we recorded sex, age, the ward where the patient was hospitalized, the drug suspected of involvement, the indication for the prescription, the site of the initial infection, the site of the worsening observed, the type of worsening, the need for admission to the intensive care unit, the concomitant drugs throughout the complication, the type of NSAID administration (self-medication or not), the outcome (resolved, sequelae, death), the alternating prescription of paracetamol and NSAIDs and the time to onset.

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Due to the small number of patients, we did not have the possibility to perform a multiple comparisons analysis and had to rely on a descriptive analysis. Quantitative variables are described as mean ± standard deviation (SD) and qualitative variables as number and percentage. All analysis were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results and Discussion

In total, 28 cases of worsening were identified (Table 1). Average age was 35±28 years; the youngest patient was 1 year old, while the oldest was 78 years old. The average age of the cases from the Infectious Diseases ward was 56 ± 16 years and 6.5± 4 years for patients from the Pediatric unit. The overall sex ratio was 0.6 (0.56 in Infectious Diseases; 0.67 in the Pediatric unit). The most frequently involved NSAIDs were ibuprofen (n=16), diclofenac (n=4), ketoprofen (n=3), tiaprofenic acid (n=1) and niflumic acid (n=1). In three cases, the NSAID taken by the patient was only declarative and could not be double-checked, in consequence they were not consider. The indication for NSAID use was primarily as painkillers (47%) (Dental, joint, lumbar and back pain). The second most common indication reported was as an antipyretic (35%). In a few rare cases, these two indications were combined. Other indications included headache with cough and rhinorrhea, otitis, oral mycosis and general malaise.

In our study, 16 patients were in the Infectious Diseases ward and 12 in the Pediatric unit (Table 2). In a single case, fever was the only sign of infection. The most frequent sites of the primary infection were ear/nose/throat (n=13) and lung (n=6). Other sites of index infection included urinary, digestive, cutaneous and joints. An interesting data is the difference between the sites of the primary infection and those of the worsening. The most frequent sites of worsening were cutaneous (n=9), lung (n=6) and ear/nose/throat (n=5). Urinary, digestive and joints stay the sites less common. Regarding the type of worsening (n=45), because more than one worsening per patient were possible, we noted 5 pneumonia, 5 cellulitis of the face (whose one periorbital cellulitis) and 4 otitis. In a single case we had a coma and in 3 cases we had a sepsis (whose one septic shock). The average time to worsening of infection after the exposure to NSAIDs was 6.8 ± 6.1 days, range 1-30 days. Overall, NSAIDs were taken on medical prescription in 19 cases (70%), as self-medication in 8 cases (30%), and in unknown circumstances in 1 case. Six children (21%) had taken NSAIDs in the context of a medical prescription alternating paracetamol and NSAIDs with a view to obtaining consistent analgesia throughout the day. Of notes, 4 patients (including 1 child) were taking antibiotics at the time of exposure of NSAIDs and when the worsening of infection occurred.

Four patients (14%) required admission to intensive care (whose 2 of these had taken NSAIDs as self-medication). One of these patients, aged 69 years, died from multiorgan failure of multifactorial origin, associating septic shock and cardiogenic shock, in the context of dissemination of a urinary tract infection. This patient had diabetes and urothelial carcinoma as comorbidity. The possible trigger for the worsening was urinary infection complicated by self-treatment with diclofenac. One 29-year old patient who was followed in the context of a dental pathology required admission to intensive care after developing frontotemporal empyema that caused intracranial hypertension and coma. The patient recovered albeit with neurological sequelae. The third patient, aged 15 years, who self-treated with an NSAID, had bilateral hypoxemic pneumonia. The fourth patient, aged 67 years, suffered septic shock. Finally, 24 patients (86%) had a favorable outcome, 3 patients suffered sequelae and one patient died.

Variables		**(Mean years ± s.d.)**
Age (n = 28)		35 ± 28
		N (%)
Sex (n = 28)		
	Male	11 (39)
NSAIDs (n = 25)		
	Ibuprofen	16 (64)
	Diclofenac	4 (16)
	Ketoprofen	3 (12)
	Niflumic acid	1 (4)
	Tiaprofenic acid	1 (4)
Self-treat (n = 27)		
	Yes	8 (30)
Alternating paracetamol/NSAID (n = 28)		
	Yes	6 (21)
NSAIDs indications (n = 34)		
	Pain	16 (47)
	Fever	12 (35)
	Others	6 (18)

Table 1: Characteristics of our patients.
NSAIDs: non-steroidal anti-inflammatory drugs; s.d.: standard deviation

Variables		**(Mean days ± s.d.)**
Time to onset (n = 23)		6.8 ± 6.1
		N (%)
Unit (n = 28)		
	Infectiology	16 (57)
	Pediatric	12 (43)
Intensive Care Unit required (n = 28)		
	Yes	4 (14)
Sites of index infections (n = 32)		
	ENT	13 (41)
	Lung	6 (19)
	Urinary	4 (12,5)
	Digestive	4 (12,5)
	Cutaneous	3 (9)
	Joints	2 (6)
Sites of worsening of infections (n = 28)		
	Cutaneous	9 (32)
	Lung	6 (22)
	ENT	5 (18)
	Urinary	4 (14)
	Digestive	2 (7)
	Joints	2 (7)
Outcomes (n = 28)	Resolved	24 (86)
	Sequelae	3 (11)
	Death	1 (3)

Table 2: Characteristics of the infections.
ENT: ear nose throat; s.d.: standard deviation.

Even though our sample size is limited, the series reported here shows the severity of worsening infection occurring after exposure to NSAIDs. To the best of our knowledge, no study to date has investigated worsening infection in patients of all ages, taking into consideration all types of infection and deteriorations. A similar study was performed by Leroy et al. [1] over a period of 3 years in a pediatric unit. The authors reported 32 cases of worsening infection, with an average age of 4.4 years, and the sites of infection were identical to those identified in our study, namely ear/nose/throat, skin and lungs.

Although there was a slight predominance of male patients in our study and considering our sex ratio of 0.6; sex does not appear to play a major role in the worsening of bacterial infection. The average ages observed were in line with those expected for the type of patient generally admitted to each unit, and also did not appear to play a preponderant role in the occurrence of the primary endpoint. It is noteworthy that no site of infection was predominant, but rather, our data indicate that any infection, regardless of its origin, can deteriorate abruptly after exposure to NSAIDs.

Ibuprofen was the most commonly implicated NSAID in the bacterial infection. It is difficult to assess whether incidence is truly higher, given the widespread use of this drug [2]. Despite the low number of cases in our series, there was substantial heterogeneity among the molecules involved. The mechanism of action of NSAIDs explains their efficacy but also their potential to be dangerous [3]. However, the precise biological mechanism on how the NSAIDs influence a primary infection is still controversial. On the one hand, NSAIDs inhibit cyclooxygenase 1 (COX1) and 2 (COX2). COX2 are enzymes that generate the production of prostaglandin, a mediator of inflammation, pain and fever, originating from the metabolic pathway of arachidonic acid. COX1 are also involved in inflammatory processes, although to a lesser extent. Moreover, NSAIDs induce the production of cytokines such as interleukin 1 or 6 and as tumor necrosis factor [4]. These changes in the host's inflammatory pathway could in part explain why infection can suddenly deteriorate when the patient takes NSAIDs. On the other hand, NSAIDs have an inhibitory role on the immune response like the inhibition of leukocyte adhesion or phagocytosis [5-9]. Finally, the symptoms that precede infection and lead to the diagnosis of infection are the signs that are due to inflammation and fever. The inflammation itself is an antibacterial defense mechanism of innate immunity. The goal of the NSAIDs could become their limits in an unreasonably use.

The side effects of this class of drugs are well documented, with the most common being gastro-intestinal [10], with an increased risk of gastroduodenal ulcers. Other adverse effects are also well documented, such as renal insufficiency, hypertension and interactions with other drugs [11]. The majority of patients in our series took NSAIDs on medical prescription, and the potential for worsening of infection seems to be underestimated by clinicians and patients. While the indication for NSAIDs was mainly for pain relief, it is worrying to note the prescription of NSAIDs as antipyretics. Indeed, fever is a frequent precursor of fever of bacterial origin. If the fever is reduced, there exists not only a risk of worsening the bacterial infection, but also a risk of delayed diagnosis since the reduction of the fever will mask the course of the infection. This means that it is potentially dangerous to retain this indication for these drugs as self-medication. The only warning indicated in the labelling of these drugs in France is about the potential for delayed diagnosis due to the reduction or absence of the symptoms of infection. There is no mention of the possibility of complications or worsening infection. Similarly, the idea that associating an antibiotic would protect against the risk of worsening infection should not prompt physicians to limit surveillance of these patients. In our study, some of the patients experienced acute worsening of infection while under antibiotic therapy.

In the literature, cases of worsening cutaneous infection and death have been described after exposure to NSAIDs [12-16]. In these cases, the deaths were mainly from necrotizing fasciitis, necrotizing soft tissue infection, sepsis or septic shock. Cisseet al. [17] reported a 27-fold increase in risk (odds ratio (OR) = 27; confidence interval (CI) 95% = [8-94]) of necrotizing bacterial dermo hypodermitis and necrotizing fasciitis in patients taking NSAIDs. Mikaeloff et al. [18] found that the use of NSAIDs was associated with an increased risk of severe skin and soft tissue complications of varicella zoster virus infection, mostly in children with varicella, with a rate ratio of complications related to NSAID exposure of 4.9 (CI 95% = [2.10-11.40]) in patients with varicella and 1.6 (CI 95% = [1.10,-2.40]) in patients with herpes zoster infection. Moreover, a case-control study by Le Bourgeois et al. [19] was conducted in 15 centers and enrolled 83 controls matched to 83 cases on a 3 to 15 years old population with an acute viral infection. The average age was 4.1 ± 2.3 years old for the case and the more prescribed NSAID was Ibuprofen. The study found, for children with an acute viral infection, an increased risk of empyema associated with NSAIDs exposure (OR = 2.79; CI 95% = [1.40-5.58]). In a study of 38 cases of severe necrotizing soft-tissue infection matched with 228 controls, Souyri et al. [20] reported a crude OR for exposure to NSAIDs of 67.46 (CI 95% = [16.00-284.20]) and an adjusted OR of 31.38 (CI 95% = [6.40-153.84]). In the case of the cellulitis, Bennani-Baïti et al. [21] described a case series of 70 patients with cervicofacial cellulitis (CFC) and found a dental origin of the CFC in 87%. 2 patients died from their worsening. Other clinical cases occurring in children have also been described in the literature concerning the cellulitis risk [22]. To go further, Nicot et al. [23] found that anti-inflammatories were a non-significant risk factor of worsen odontogenic cervicofacial cellulitis with an OR of 5.99 (CI 95%= [0.71-50.88]) with a 91.8% use of NSAIDs. Basille et al. [24] found a link between the intake of NSAIDs and the worsen risk of a community-acquired pneumonia (OR = 2.57; CI 95% = [1.02-6.64]). This study reported that NSAIDs importantly delayed hospital referral and delayed antibiotics consumption. Other studies have reported NSAIDs to be associated with the occurrence of pleuropulmonary complications but not the course of infection [25,26]. Indeed, Voiriot et al. [25] reported that NSAID exposure was independently associated (OR = 8.1; CI 95% = [2.30-28]) in 90 patients with community-acquired pneumonia admitted to the intensive care unit. In a retrospective review of 70 patients with pneumococcal pneumonia admitted to their intensive care unit, Messika et al. reported [26] that antimicrobial therapy was significantly delayed, and pleural effusion was significantly more frequent in the NSAID group, but there was no difference between groups in terms of clinical presentation at admission, length of stay, or ICU mortality. Le Turnier et al. [27] reported severity features of patients having bacterial infection and exposed prior to their hospitalization to a NSAID. The average age was 37 years, the ibuprofen intake in 63%, ketoprofen in 24% and diclofenac in 20%. The main sites of infection were in this study, respiratory system and skin/soft tissue. The authors reported one septic shock and 10 sepsis. In two other studies [28], no statistically significant link was observed in the context of severe sepsis and septic shock.

Conclusion

Despite the important limits of our study, it warns however about the increased risk of worsening of bacterial infections after exposure to NSAIDs; both in adult and in pediatric patients and for all types

of infections. Given that many other molecules exist that have analgesic and antipyretic properties, the risk-benefit ratio associated with NSAIDs in case of suspected bacterial infection seems to be not in favor of their use in this indication, or at least without specific precautions, awareness and information on the risks. It would appear preferable to use another drug class with the same indications, such as paracetamol, to avoid the risk of deterioration and to balance the possible benefit of a NSAID regarding the potential worsening of infection and complications. Again, because NSAIDs importantly delayed hospital referral and delayed antibiotics consumption, awareness should be raised among physicians and patients about the potential hazards of taking NSAIDs. Large-scale epidemiological studies would make it possible to evaluate more specifically the risk associated with the use of NSAIDs for self-treatment. The reassuring and uninformative nature of some package inserts for NSAIDs regarding the precautions to be taken, and the risk of adverse events justifies review and updating of the contents of the labelling for these drugs. Our study aims to alert once more, in view of the number and seriousness of the cases we have collected, to the lack of transparency of the secondary infectious risk of NSAIDs.

Competing Interests

The authors declare that they have no competing interests.

Author's Contributions

QJ, FK and BA conceived the study. QJ managed the data, conducted the analyses and wrote the methods and the results with contributions from BA and TT. TT took lead authorship of the paper with contributions from QJ, FK, BAand AM. All authors have approved the final version of the manuscript.

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