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Nonsteroidal anti-inflammatory drug use and the risk of severe skin and soft tissue complications in patients with varicella or zoster disease

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Three previous epidemiological studies found an increased risk of severe skin and soft tissue infectious complications associated with exposure to NSAIDs in children with varicella.
- *In vitro* studies demonstrated that decreases in defences against infections induced by NSAIDs could be due to impairment of neutrophil blood cell function.

WHAT THIS STUDY ADDS

- The use of NSAIDs is associated with an increased risk of severe skin and soft tissue complication of varicella in children.
- The use of NSAIDs is also associated with a small increased risk of such complications in zoster disease in adults and the elderly.
- This study supports the limited prescription of NSAIDs in VZV infection.

AIMS

To assess the risk of severe skin and soft tissue complications associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in treating patients with varicella zoster virus infection.

METHODS

The design was a nested case-control study, with matching for age and practice. The setting was primary care in the United Kingdom (United Kingdom's General Practice Research Database). Two population-based cohorts of all patients with a primary varicella ($n = 140\,111$) or zoster ($n = 108\,257$) diagnosis during 1994–2005 were followed up for 2 months after diagnosis. Main outcome measures of severe skin or soft tissue complications (mostly cellulitis and abscess) associated with current NSAID or paracetamol use were estimated, and adjusted for potential confounding factors, including sex, drug use, and comorbidity.

RESULTS

In patients with varicella, there were 386 cases of severe skin or soft tissue complications (rate 2.8 per 1000) during the 2 month follow-up period (mean age 10.7 years). The rate of complications associated with exposure to NSAIDs was increased (rate ratio 4.9; 95% CI 2.1, 11.4). In patients with zoster disease, there were 681 cases of severe skin or soft tissue complications (rate 6.3 per 1000) during the 2 month follow-up (mean age 60.9 years). The rate ratio of complications associated with exposure to NSAIDs was 1.6 (95% CI 1.1, 2.4). In both conditions, there was no increased risk of complication associated with a current exposure to paracetamol.

CONCLUSIONS

The use of NSAIDs is associated with an elevated risk of severe skin and soft tissue complications of varicella zoster virus infection, mostly in children with varicella.

Introduction

Complications of varicella zoster virus (VZV) infection are rare [1–5]. After reports of severe skin or soft tissue complications in children with varicella, the potential risk of worsening VZV infection associated through use of non-steroidal anti-inflammatory drugs (NSAIDs) was questioned. More data are needed from rigorously designed epidemiological studies to answer the question [6, 7].

The previous studies, either case series or epidemiological studies, focused on necrotizing fasciitis related to severe invasive group A streptococcal infections in children with varicella [8–14]. Case series, which reported the temporal sequence between exposure and event did not provide sufficient proof for causality. Randomized controlled trials did not have a sufficient number of subjects to conclude about these complications [8, 9]. However, epidemiological studies demonstrated an increased risk associated with the use of NSAIDs, with conflicting interpretations [10–12].

Concerning necrotizing fasciitis in all age groups, with or without VZV infection, a recent review concluded that 'prospective studies do not support a risk of developing group A streptococcal necrotizing fasciitis as a result of NSAID therapy, or a worsening of established streptococcal infection' [15]. Another study found an association between use of NSAIDs and an increased risk of community-acquired *Clostridium difficile*-associated disease in adults [16]. *In vitro* studies demonstrated decreases in neutrophil function after exposure to NSAIDs [17, 18]. These data supported the hypothesis of a decrease in defence against infections associated with NSAIDs.

In view of these conflicting data, we conducted a population-based epidemiological study to determine whether NSAIDs could increase the risk of severe skin or soft tissue complications in patients with varicella or zoster disease.

Methods

Subjects and source of data

The study cohorts were identified from the population-based General Practice Research Database (GPRD), which has been described in detail elsewhere [19, 20]. More than 3 million people in the United Kingdom are enrolled with over 400 general practitioners who use office computers and have agreed to provide data for research purposes. General practitioners have been trained to record medical information including demographic data, medical diagnoses, details of hospital stays, and death using a standard anonymous form. The physicians generate prescriptions directly with their study computer; this information is automatically transcribed into the computer record. A modification of the Oxford Medical Information System classification (similar to the International Classification of Diseases, Eighth Revision) is used to enter medical diagnoses, and a coded drug dictionary based on the UK Prescription Pricing Authority Dictionary is used for recording prescriptions. The recorded information on drug exposure and diagnoses has been validated and proven to be of high quality [21–23]. The study was approved by the Scientific and Ethical Advisory Group of the GPRD.

We formed two cohorts, one of all patients with a first primary varicella diagnosis ($n = 156\,034$) (cohort 1: time zero for inclusion was taken as the date on which the code for primary varicella was recorded), the other with a first zoster disease diagnosis ($n = 129\,684$) (cohort 2: time zero for inclusion was taken as the date on which the code for zoster disease was recorded), between January 1, 1994 and December 31, 2005. For both cohorts, subjects with chronic hepatic insufficiency or chronic renal insufficiency at any time prior to the date of this first diagnosis (cohort entry) were excluded ($n = 155\,910$ in cohort 1, $n = 127\,628$ in cohort 2). The subjects were followed from the date of cohort entry for up to 2 months or until the occurrence of the study outcome (severe skin or soft tissue complication defined below). We excluded subjects with follow-up under 2 months. Thereafter, we were able to study a final cohort 1 of 140 111 subjects and a final cohort 2 of 108 257 subjects. We used a nested case-control design within each cohort to test for association between use of NSAIDs and severe skin or soft tissue complications and to allow precise assessment of the changes over time in the use of drugs.

Cases

All severe skin or soft tissue complications that occurred during the 2 month follow-up were identified using GPRD medical codes. These included cellulitis, abscess, fasciitis or necrosis. The date of the first occurrence of this outcome during the 2 month follow-up was designated the index date.

Controls

Each case was matched with up to a maximum of 10 controls within its cohort of origin for age (± 2 years) to control for possible age-related confounding and for general practice to control for possible physician-related and geographical variations. In addition, to control for trends over time in the use of drugs, they were matched for the calendar year of cohort entry, and controls had to have a follow-up at least as long as the case to control for delay of disease occurrence. The matched control was assigned the index date of the case. We matched for all factors, but not for general practice for 19 case patients from the varicella cohort (cohort 1) and 51 cases from the zoster cohort (cohort 2), for whom no controls could be found.

Exposure assessment

We identified all NSAID prescriptions given during follow-up. These included acemetacin, celecoxib, diclofenac,

diflunisal, etodolac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, meloxicam, nabumetone, naproxen, piroxicam, rofecoxib, sulindac, tenoxicam and tiaprofenic acid. We also identified prescriptions for paracetamol. We considered that the first 2 days of exposure could not cause complications and could potentially induce misclassification [17, 18]. Current exposure to NSAIDs or paracetamol was thus defined as a prescription during the 3–30 days before the index date.

Statistical analysis

All analyses were stratified by cohort. Conditional logistic regression for matched case-control data was used to estimate the adjusted rate ratios of severe skin or soft tissue complications in each cohort of varicella or zoster disease (with their 95% confidence intervals) which were associated with the current use of NSAIDs or paracetamol. The noncurrent users were the reference group. In addition to the inherent adjustment by the matched factors, we adjusted for sex, as well as the following medication covariates recorded in the year before the index date: the number of prescriptions for: antibiotics (penicillins, cephalosporins, cephamycins and other beta-lactams, sulphonamides and trimethoprim, macrolides, tetracyclines, quinolones, metronidazole and tinidazole), aspirin, corticosteroids (systemic or local use) [24], vaccines, immunosuppressive drugs (immunosuppressants or antiproliferative drugs). We also adjusted for gastrointestinal disorders and chronic diseases including rheumatologic inflammatory diseases (rheumatoid arthritis, lupus), cancer (solid tumours), leukaemia, lymphoma, diabetes (diabetes insipidus excluded), cystic fibrosis, leucopenia, lymphopenia, neutropenia, immune deficiency (including HIV infection, bone marrow and other transplantations, except liver and renal transplants, which were exclusion criteria, hypogammaglobulinaemia and septic granulomatosis).

Results

We identified a cohort of 140 111 subjects with a first occurrence of varicella diagnosis between January 1, 1994 and December 31, 2005 (cohort 1). The mean age at cohort entry was 10.7 (SD 14.5) years. In the same period, we identified a second cohort of 108 257 subjects with a first occurrence of zoster disease diagnosis, with mean age of 60.9 years (SD 20.7) (cohort 2).

Within patients with varicella, 386 had a skin or soft tissue complications during the 2 month follow-up (rate 2.8 per 1000). These included cellulitis ($n = 271$, 70.2%), abcess ($n = 107$, 27.7%), and fasciitis ($n = 7$, 1.8%), as well as one case with a necrosis code. These cases were matched with 2402 controls from the cohort. Within patients with zoster disease, 681 had a skin or soft tissue complication during the 2 month follow-up (rate 6.3 per 1000). These included cellulitis ($n = 514$, 75.5%), abcess ($n = 118$, 17.3%) and fasciitis ($n = 47$, 6.9%), as well as two cases with necrosis. These cases were matched with 2142 controls from the cohort. Baseline characteristics of the case patients and controls, considered for adjustment, are reported in Table 1. Gastrointestinal disorders were more common among cases in both cohorts, as were other comorbidities. In cohort 1, the proportion of subjects that were using both NSAIDs and paracetamol concurrently (current exposure) was small: $n = 2$ (0.52%) among cases and $n = 7$ (0.29%) among controls. In cohort 2, the proportion of the subjects that were using both NSAIDs and paracetamol concurrently (current exposure) was also small: $n = 18$ (2.64%) among cases and $n = 49$ (2.29%) among controls.

Table 2 presents the crude and adjusted rate ratios of severe skin or soft tissue complication in relation to the use of NSAIDs or paracetamol 3–30 days before the index date. Among patients with varicella, 3.11% of the cases and 0.58% of the controls had a current exposure to NSAIDs,

Table 1

Characteristics of the study subjects within each cohort studied

Variables	Primary varicella Cases ($n = 386$)	Matched controls ($n = 2402$)	Zoster disease Cases ($n = 681$)	Matched controls ($n = 2142$)
Age mean years (SD)	10.7 (14.5)	11.4 (15.0)	60.9 (20.7)	61.0 (20.6)
Female *n* (%)	184 (47.67)	1180 (49.13)	417 (61.23)	1340 (62.56)
Gastrointestinal disorder *n* (%)	8 (2.07)	26 (1.08)	52 (7.64)	68 (3.17)
Rheumatologic inflammatory diseases* or cancer or leukaemia or lymphoma *n* (%)	2 (0.52)	2 (0.08)	29 (4.26)	42 (1.96)
Diabetes or cystic fibrosis *n* (%)	6 (1.55)	9 (0.37)	43 (6.31)	90 (4.20)
Leucopenia, lymphopenia, neutropenia, immune deficiency *n* (%)	0	0	0	1
Aspirin, mean number of prescriptions (SD)	0	0.03 (0.44)	0.81 (2.57)	0.75 (2.43)
Antibiotics, mean number of prescriptions (SD)	0.23 (0.42)	0.22 (0.41)	0.23 (0.42)	0.17 (0.38)
Corticosteroids, mean number of prescriptions (SD)	0.11 (0.32)	0.11 (0.31)	0.15 (0.36)	0.09 (0.29)
Vaccines, mean number of prescriptions (SD)	0.05 (0.22)	0.03 (0.18)	0.15 (0.35)	0.14 (0.35)
Immunosuppressants and antiproliferative drugs, mean number of prescriptions (SD)	0.002 (0.051)	0	0	0

*Rheumatoid arthritis or systemic lupus erythematosus.

Table 2

Crude and adjusted rate ratios of skin or soft tissue complication associated with current use (3–30 days before the index date) of NSAIDs and paracetamol among varicella or zoster patients (reference no current use)

Variables	Cases	Matched controls	Crude RR	Adjusted RR* (95% CI)
Primary varicella				
Number of subjects	386	2402		
Current use of:				
NSAIDs %	12 (3.11)	14 (0.58)	5.2	4.9 (2.1, 11.4)
Paracetamol %	51 (13.21)	246 (10.24)	1.7	1.5 (1.0, 2.2)
Zoster disease				
Number of subjects	681	2142		
Current use of:				
NSAIDs %	57 (8.37)	113 (5.28)	1.6	1.6 (1.1, 2.4)
Paracetamol %	146 (21.44)	537 (25.07)	0.8	0.8 (0.6, 1.0)

RR, rate ratio. *Adjusted for all variables in Table 1.

which consisted mostly of ibuprofen (85%). The adjusted rate ratio of complication associated with exposure to NSAIDs was 4.9 (95% CI 2.1, 11.4). Within patients with zoster disease, 8.37% of the cases and 5.28% of the controls had a current exposure to NSAIDs (92% ibuprofen). The adjusted rate ratio of complication associated with exposure to NSAIDs was 1.6 (95% CI 1.1, 2.4). The rate ratios associated with paracetamol use were 1.5 (95% CI 1.0, 2.2) among varicella patients and 0.8 (95% CI 0.6, 1.0) among patients with zoster.

Discussion

We found that the use of NSAIDs was associated with an increased risk of severe skin and soft tissue complications in varicella, which mostly includes children. Our data also suggest that there was a smaller increase in the risk of these complications associated with NSAIDs in patients with zoster disease, which includes mainly adults and elderly.

Previous case series and epidemiological studies focused on necrotizing fasciitis, related to severe invasive group A streptococcal infections, in children with varicella [8–14]. Cases series, which reported the temporal sequence between exposure and event did not have sufficient support for causality. Randomized controlled trials did not enrol a sufficient number of subjects to conclude about these complications [8, 9].

Three previous epidemiological studies (cohort or case-control studies) demonstrated the same trends as ours. A cohort study among an automated database of health maintenance organization in USA, demonstrated a three fold increase of risk of skin and soft tissue superinfection associated with ibuprofen use in the month prior to varicella in children, compared with no use in the period [10]. The two other were case-control field studies. The first focused on necrotizing fasciitis [11]. Cases (previously healthy children hospitalized for a necrotizing fasciitis within 3 weeks of the onset of varicella) were more likely than controls (previously healthy children hospitalized for another soft tissue infection within the same period of the onset of varicella) to have used ibuprofen in the time before the index date (OR 11.5, 95% CI 1.4, 96.9). In the second, cases (necrotizing soft tissue infections or other invasive group A streptococcal (GAS) infection within 2 weeks of onset of varicella) were more likely than controls (children with primary varicella infection who did not develop invasive GAS infection, recruited among primary care physicians) to have used ibuprofen (most frequently associated with acetaminophen (paracetamol) 7 days before the index date (OR 3.9, 95% CI 1.3, 12), compared with acetaminophen (paracetamol) alone [12].

Coincident with the increased frequency of severe, invasive group A streptococcal infection, mostly in North America, numerous case reports have linked necrotizing fasciitis with the use of NSAIDs even without primary varicella [25]. Moreover, a recent study found an association between use of NSAIDs and an increased risk of community-acquired *Clostridium difficile*-associated disease in adults [16]. These reports, along with *in vitro* studies demonstrating decreases in neutrophil function after exposure to NSAIDs, suggest that NSAIDs may play a role, not only in the cause of varicella-associated necrotizing fasciitis, but in general worsening of infections [17, 18, 26–28]. More specifically, human blood neutrophils exposed to appropriate stimuli aggregate, degranulate and generate superoxide anion. These functions are involved in defence against infectious diseases and could be decreased by NSAIDs exposure. For example, in the Kaplan *et al.* study [26], neutrophils from subjects taking therapeutic doses of ibuprofen, indomethacin, or piroxicam showed profiles of inhibited responses to a chemoattractant similar to those observed with these agents *in vitro*. These data suggest that NSAIDs may inhibit neutrophil functions, either aggregation or degranulation, both *in vitro* and *in vivo*. Other studies confirmed that NSAIDs

induced *in vitro* a marked inhibition in adherence of neutrophils [27]. Another mechanism of immune suppression induced by NSAIDs, that could predispose patients to infectious complications, could be inhibition of prostaglandin synthesis [18, 28].

The use of a nested case-control study in a database such as GPRD, i.e. a cohort study, has several strengths [19–23, 29]. One is the population-based nature of the data source and the size of the study. Moreover, matching on calendar time and practice allows control for time-dependent, physician-related and geographical variations in the outcome and exposure. The design also minimizes the bias due to inappropriate selection of controls, and the use of prospectively recorded computerized exposure records prevents recall bias. Other types of differential misclassification of exposure history are also unlikely because exposure information was gathered prospectively before the first symptoms of the complicated disease.

It was also adjusted for various known or suspected risk factors for complicated VZV disease which could be confounding. Although varicella typically follows an uncomplicated course in children, adults and immunocompromised patients can develop complications involving several organs; some complications may be fatal [30, 31]. We performed adjustment on risk factors for infectious disease and on treatment use for infectious disease. Confounding by indication (fever treatment related to onset of varicella or zoster disease) could explain part of the results. The extent of this bias is however, unlikely when comparing the effects of NSAIDs and paracetamol, particularly stratified by varicella and zoster disease. Because of small numbers of patients using both NSAIDs and paracetamol we cannot deduce that the use of one was favoured over the other.

A certain degree of nondifferential (random) misclassification of exposure history is possible as a proportion of persons might have received the exposure without their GP's knowledge by over-the-counter medications for NSAIDs and paracetamol, despite facilities for reimbursement in the UK health care system. However, this should have reduced the size of the effect, thereby attenuating the association between exposure and complicated disease. Therefore, any result found by this study could be considered a lower bound estimate of the effect. Therefore, any result found by this study could be considered a lower bound estimate of the effect. Moreover, despite possible over-the-counter medications for NSAIDs and paracetamol, not recorded in the GPRD database, we considered that this would represent a small number of subjects, and be of the same magnitude in patients with and without complications. Indeed, primary varicella and zoster disease are diseases that provoke concern, with fever, rash, itching or pain, which require consultation with a physician in the vast majority of patients [5]. Antipyretic treatments and anti-itching treatments are often requested by patients, as is the exact diagnosis. Fever, which is the reason for prescription of antipyretics, is not correlated with severity of symptoms on presentation, namely rash and itching or pain. Moreover, because exposure was studied before occurrence of complications, at the beginning of the inclusion, and thus complications could not occur concurrently with inclusion, but only after several days of disease progression, prescription bias was reduced. Previous studies were performed about exposure to NSAIDs or paracetamol, using the UK GPRD with good reliability [16, 23].

The frequency of complications with VZV was rare in our study and was concordant with the literature [1–4]. Abscess is a rare but described complication of VZV infection [32]. In zoster disease skin and soft tissue superinfections are less frequent than in varicella [1]. The combined outcome of complications could have attenuated the strength of the association between exposure and complicated disease. Recording issues of the GPRD could have caused some degree of underestimation for some outcomes. Some of the more specific diagnosis (such as for necrotizing fasciitis) may be under-reported especially if the patient ends up in the hospital emergency room instead of at the general practice and the physician chooses to record the reason for the emergency room visit in the free text instead of with a code for the medical event. However, we considered that such underestimation will be nondifferential between users of NSAIDs or paracetamol.

An important reduction in paediatric morbidity and mortality rates related to varicella, including invasive group A streptococcal infections, was seen in the USA, after the launch of a universal vaccination programme in 1995, among 12–18 month old infants, with 75% decreases in varicella-related hospitalizations and deaths [33, 34]. Despite this important impact, coverage was not total in the USA and the project has not been systematically implemented worldwide, including Europe [35].

We recommend that the prescription of NSAIDs be limited in VZV infections. Nevertheless, because of the limitations of this observational study, further epidemiological studies, using databases designed to take into account over-the-counter medications more accurately, would be useful. Moreover, further studies are needed to assess the risk of complications of other infectious diseases in relation to exposure to NSAIDs.

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