Non-steroidal anti-inflammatory drugs and the risk of *Clostridium difficile*-associated disease

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Increasing age, length of hospital stay and previous antibiotic use have been established as important risk factors in the development of *Clostridium difficile* associated disease (CDAD). Several case reports over the past 30 years have linked diclofenac, a non-steroidal anti-inflammatory drug (NSAID) with CDAD. We assessed whether NSAID use in general, and diclofenac use in particular, is associated with an increased risk of CDAD.

WHAT THIS STUDY ADDS

- In this population based study, the use of diclofenac was associated with a 35% increase in the risk of developing CDAD. This association persisted when we limited the analysis to non-hospitalized patients. No association was found between the use of any other NSAIDs and the risk of CDAD.

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AIM

Several case reports have linked diclofenac, a non-steroidal anti-inflammatory drug (NSAID), with *Clostridium difficile* associated disease (CDAD). We assessed whether NSAID use in general, and diclofenac use in particular, is associated with an increased risk of CDAD.

METHODS

We used the United Kingdom's General Practice Research Database (GPRD) to conduct a population-based case-control study. All cases of CDAD occurring between 1994 and 2005 were identified and were matched to 10 controls each. Conditional logistic regression was used to estimate the odds ratio of CDAD associated with current NSAID use, adjusting for covariates.

RESULTS

We identified 1360 CDAD cases and 13 072 controls. We found an increased risk of CDAD associated with diclofenac (adjusted odds ratio (RR) 1.35, 95% confidence interval (CI) 1.10, 1.67). We did not observe an increased risk of CDAD with use of any other NSAID. No dose-response for diclofenac exposure was found. When we analyzed only patients who were not hospitalized in the year before the index date, we found diclofenac to have a similar effect on CDAD risk (adjusted RR 1.43, 95% CI 1.11, 1.84).

CONCLUSION

Diclofenac use is associated with a modest increase in the risk of CDAD. In patients at risk of CDAD, other NSAIDs could be prescribed.

Introduction

Clostridium difficile is the leading cause of hospital-acquired enteric infection in developed countries [1]. Increasing age, length of hospital stay and previous antibiotic use have been established as important risk factors in the development of *Clostridium difficile* associated disease (CDAD) [2]. Until recently, CDAD was believed to be important only as a nosocomial disease causing very few and mostly benign cases in the otherwise healthy community dwellers [3]. However, recent studies have been implicating *C. difficile* as an ever more significant cause of diarrhoea in the community [4]. Indeed, there has been an exponential increase in the incidence of cases diagnosed in the community from less than 1 per 100 000 persons in 1994 to 22 per 100 000 in 2004, in the United Kingdom. A growing number of these cases are emerging in the community from persons who are healthy, non-hospitalized and even unexposed to antibiotic treatment [5, 6]. In a recent study of the association between gastric acid-suppressive agents and the risk of community-acquired CDAD, an unexpected finding was made, implicating NSAID use as a risk factor for CDAD [adjusted odds ratio (RR), 1.3; 95% CI 1.2–1.5] [2]. In that study, however, NSAIDs were undifferentiated. Furthermore, several case reports over the past 30 years have suggested an association between diclofenac use and CDAD [7]. [8], [9], We sought to explore the association between NSAIDs and CDAD, and if diclofenac was any different from other NSAIDs with respect to the risk.

Methods

Data source and study design

The data for this study was obtained from the United Kingdom General Practice Research Database (GPRD). This dataset was from an older version of the GPRD, obtained for use with a previous study [2], and so lacked information available in more modern GPRD datasets (including hospitalization information). Information collected from participating general practitioners includes: demographics, medical symptoms, signs and diagnoses, all prescriptions, treatment outcomes, referrals to hospitals or specialists, laboratory tests, pathology results and lifestyle factors (height, weight, BMI, smoking and alcohol consumption). A modification of the Oxford Medical Information System classification is used to standardize the medical diagnoses and a coded drug list based on the UK Prescription Pricing Authority Dictionary is used for the recording of prescriptions. Several studies have evaluated the recorded information on diagnoses and drug exposure, which have proven to be highly reliable and valid [10–12]. We used a case-control design with all cases of CDAD including both hospital and community acquired cases identified in the database.

Case definition

Cases of CDAD were defined as having a first clinical diagnosis of CDAD, a first laboratory diagnosis of CDAD or a first prescription of oral vancomycin, its only indication being CDAD [13], between January 1 1994 and December 31 2005. Only first events were included as cases to ensure that the patient was not being treated for a recurrence of CDAD [2, 14]. The index date for included cases was the date of their first CDAD event. Cases had to be aged 18 years or older and have at least 2 years of records in the GPRD prior to the date of diagnosis to be entered into the study.

Control selection

For each case, up to 10 controls (both cases and controls were aged 18 years and older) were randomly selected from patients attending the same medical practice as the case, matched on age ± 2 years), who had not received a prescription for oral vancomycin and were neither toxin positive nor had a clinical diagnosis of *C. difficile* recorded by the time the case was diagnosed (index date). We matched on medical practice to control for possible physician-related or practice related recording differences and geographical variation in the exposure.

Covariates

The following potential confounders were identified. Age and physician practice were already matching factors, to which gender was added as a covariate. In addition, the presence of the following gastro-intestinal diseases in the 2 years prior to the index date was determined from diagnoses entered by the general practitioner: acid reflux disease, inflammatory bowel disease, diverticular disease, gastro-intestinal bleed and peptic ulcer disease. Other physician diagnoses for co-morbid conditions present at any time prior to the index date included cancer, chronic obstructive pulmonary disease, congestive heart failure, dementia, diabetes mellitus, heavy alcohol consumption, liver failure, myocardial infarction, renal failure and stroke [2].

Other covariates included medications associated with the risk of CDAD, which included any antibiotic, H₂-receptor antagonist, proton pump inhibitor and oral corticosteroid, given in the 90 days prior to the index date [2].

Statistical analyses

The primary analysis was based on conditional logistic regression to obtain an odds ratio which can be interpreted as an estimate of the rate ratio of CDAD with regards to NSAID use. Patients were classified as currently exposed to NSAIDs if they received a prescription for any NSAID in the 90 day period prior to the index date, in order to capture both constant and intermittent use of these agents almost exclusively prescribed for inflammatory pain relief, otherwise they were considered unexposed.

The adjusted odds ratio (RR) of CDAD was estimated for current use of all NSAIDs after adjustment for gender, co-morbidities and co-prescriptions. The secondary analysis used conditional logistic regression to evaluate the association between current use of individual NSAIDs and development of CDAD. Furthermore, a dose-response analysis was performed using the number of prescriptions for each NSAID in the 180 day period prior to the index date, among current users. We defined the dose-response exposure measure based on its distribution as either less than five or more than five prescriptions in the 180 days prior to the index date.

Finally, a sensitivity analysis was performed to assess the effect of hospitalization in the year prior to the index date. All analyses were performed using SAS statistical software, version 9.1.3.

Results

In all, 1360 cases were found, the majority of which (63.5%) were identified through clinical diagnosis. Each case was matched to a maximum of 10 controls, for a total of 13 072 controls. There was no significant difference ($P = 0.35$) in gender between cases (48%) and controls (49%). The age distribution and distribution of index dates were identical in the cases and controls.

Table 1 compares the covariate distributions in the cases and controls. Overall, cases had a higher prevalence

Table 1

Clinical characteristics of cases and controls

	Cases	Controls	P value
Number of subjects	1 360	13 072	
Gastro-intestinal diseases in the 2 years prior to the index date			
Acid reflux	78 (5.7%)	475 (3.6%)	0.0001
Inflammatory bowel disease	67 (4.9%)	73 (0.56%)	<0.0001
Diverticular disease	53 (3.9%)	345 (2.6%)	0.0070
Gastrointestinal bleeding	44 (3.2%)	128 (0.98%)	<0.0001
Peptic ulcer	3 (0.22%)	18 (0.14%)	0.45
Other diseases any time prior to the index date			
Cancer	60 (4.4%)	234 (1.8%)	<0.0001
Chronic obstructive pulmonary disease	133 (9.8%)	542 (4.2%)	<0.0001
Congestive heart failure	158 (11.6%)	596 (4.6%)	<0.0001
Dementia	43 (3.2%)	244 (1.9%)	0.0011
Diabetes	150 (11.0%)	1 055 (8.1%)	0.0002
Heavy alcohol consumption	22 (1.6%)	94 (0.72%)	0.0004
Liver failure	5 (0.37%)	15 (0.11%)	0.017
Myocardial infarction	49 (3.6%)	221 (1.7%)	<0.0001
Renal failure	71 (5.2%)	145 (1.1%)	<0.0001
Stroke	59 (4.3%)	267 (2.0%)	<0.0001
Medications in the 90 days prior to the index date			
Any antibiotic	681 (50.1%)	2 218 (17.0%)	<0.0001
Any H ₂ -receptor blocker	86 (6.3%)	515 (3.9%)	<0.0001
Any proton pump inhibitors	356 (26.2%)	1 463 (11.2%)	<0.0001
Oral corticosteroids	3 (0.22%)	5 (0.04%)	0.0065

of gastro-intestinal diseases and conditions when compared with controls. In particular, cases were significantly and much more likely to have inflammatory bowel disease and gastro-intestinal bleeding than controls. Cases were also more prone to other diseases, such as cancer, chronic obstructive pulmonary disease (COPD), congestive heart failure, myocardial infarction and renal failure. Diabetes was also significantly more common in cases. Finally, cases had a much higher exposure to antibiotics, H₂-receptor blockers, oral corticosteroids and proton pump inhibitors, in the 90 days preceding the index date.

To assess further the potential confounding effects of the covariates, Table 2 describes these risk factors according to exposure. These comparisons were made in the controls which are representative of the study population. Among the 13 072 controls, 9363 were not prescribed an NSAID in the 90 days prior to the index date, while 3709 were. Of all the NSAIDs being studied, acetylsalicylic acid was by far the most frequent drug exposure with 2656 controls having received at least one prescription during the 90 days time window, followed by diclofenac with 547 exposed controls.

Besides differences in comorbidity, NSAID users, including diclofenac and Cox-2 inhibitor users, were more likely than unexposed controls to have been prescribed an antibiotic, an H₂-receptor blocker or a proton pump inhibitor in the 90 days prior to the index date.

This could be explained by the tendency to prescribe gastric acid suppressants and Cox-2 inhibitors to patients who need anti-inflammatory medications, but are at risk of gastro-intestinal bleed.

Table 3 shows that the adjusted RR of CDAD associated with any current NSAID exposure was 0.97 (95% CI 0.86, 1.10). Of all NSAIDs, only diclofenac was found to be significantly associated with an increased risk of CDAD (adjusted RR 1.35, 95% CI 1.10, 1.67). In the dose-response analysis among current users, less than five prescriptions (adjusted RR 1.35, 95% CI 1.02, 1.79) as well as those with five or more prescriptions (adjusted RR 1.35, 95% CI 1.00, 1.82) were associated with an increased risk of CDAD.

The analysis restricted to patients who were not hospitalized in the year before the index date found a similar effect of diclofenac (adjusted RR 1.43, 95% CI 1.11, 1.84 (Table 4). In this non-hospitalized subgroup, diclofenac use of less than five prescriptions (adjusted RR 1.39, 95% CI 1.00, 1.95) as well as five or more prescriptions (adjusted RR 1.47, 95% CI 1.01, 2.12) was associated with an increased risk of CDAD.

Discussion

In this population based study, the use of diclofenac was associated with a 35% increase in the risk of developing CDAD. This association persisted when we limited the

Table 2

Clinical characteristics of controls according to NSAID exposure in the 90 days prior to the index date

	Exposed		Traditional NSAIDs					Other traditional NSAIDs	Cox-2 inhibitors	Acetyl-salicylic acid
	Unexposed	Any traditional NSAID	Diclofenac	Ibuprofen	Naproxen					
Number of controls (13 072)	9 363	3 709	547	446	108	262	116	2 656		
Gastrointestinal diseases in the two years prior to the index date										
Acid reflux	309 (3.3%)	166 (4.5%)	19 (3.5%)	25 (5.6%)	6 (5.6%)	17 (6.5%)	4 (3.5%)	106 (4.0%)		
Inflammatory bowel disease	52 (0.56%)	21 (0.57%)	3 (0.55%)	2 (0.45%)	0 (0.0%)	3 (1.2%)	0 (0.0%)	17 (0.64%)		
Diverticular disease	220 (2.4%)	125 (3.4%)	18 (3.3%)	11 (2.5%)	2 (1.85%)	14 (5.3%)	5 (4.3%)	96 (3.6%)		
Gastrointestinal bleeding	90 (0.96%)	38 (1.0%)	2 (0.37%)	4 (0.90%)	0 (0.0%)	3 (1.2%)	1 (0.86%)	30 (1.1%)		
Peptic ulcer	12 (0.13%)	6 (0.16%)	0 (0.0%)	2 (0.45%)	0 (0.0%)	1 (0.38%)	0 (0.0%)	5 (0.19%)		
Other diseases any time prior to the index date										
Cancer	149 (1.6%)	85 (2.3%)	15 (2.7%)	14 (3.1%)	0 (0.0%)	4 (1.5%)	1 (0.86%)	66 (2.5%)		
Chronic obstructive pulmonary disease	342 (3.7%)	200 (5.4%)	20 (3.7%)	13 (2.9%)	8 (7.4%)	5 (1.9%)	6 (5.2%)	168 (6.3%)		
Congestive heart failure	296 (3.2%)	300 (8.1%)	24 (4.4%)	19 (4.3%)	5 (4.6%)	14 (5.3%)	2 (1.7%)	260 (9.8%)		
Dementia	153 (1.6%)	91 (2.5%)	5 (0.91%)	7 (1.6%)	1 (0.93%)	5 (1.9%)	1 (0.86%)	82 (3.1%)		
Diabetes	556 (5.9%)	499 (13.5%)	58 (10.6%)	44 (9.9%)	10 (9.3%)	24 (9.2%)	10 (8.6%)	414 (15.6%)		
Heavy alcohol consumption	69 (0.74%)	25 (0.67%)	3 (0.55%)	3 (0.67%)	4 (3.7%)	0 (0.0%)	1 (0.86%)	16 (0.60%)		
Liver failure	14 (0.15%)	1 (0.03%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.04%)		
Myocardial infarction	51 (0.54%)	170 (4.6%)	10 (1.8%)	9 (2.0%)	1 (0.93%)	8 (3.1%)	5 (4.3%)	160 (6.0%)		
Renal failure	67 (0.72%)	78 (2.1%)	9 (1.7%)	7 (1.6%)	1 (0.93%)	5 (1.9%)	4 (3.5%)	60 (2.3%)		
Stroke	95 (1.0%)	172 (4.6%)	13 (2.4%)	4 (0.90%)	2 (1.9%)	6 (2.3%)	1 (0.86%)	161 (6.1%)		
Medications in the 90 days prior to the index date										
Any antibiotic	1 391 (14.9%)	827 (22.3%)	123 (22.5%)	94 (21.1%)	26 (24.1%)	72 (27.5%)	29 (25.0%)	603 (22.7%)		
Any H ₂ -receptor blocker	296 (3.2%)	219 (5.9%)	36 (6.6%)	18 (4.0%)	12 (11.1%)	34 (13.0%)	8 (6.9%)	148 (5.6%)		
Any proton pump inhibitors	831 (8.9%)	632 (17.0%)	99 (18.1%)	72 (16.1%)	8 (7.4%)	44 (16.8%)	28 (24.1%)	480 (18.1%)		
Oral corticosteroids	4 (0.04%)	1 (0.03%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.04%)		

Table 3

Crude and adjusted odds ratios (RR) of CDAD associated with NSAID exposure in the 90 days prior to the index date

NSAIDS exposure in the 90 days prior to the index date	Cases	Controls	Crude RR	Adjusted* RR	95% CI
Any traditional NSAID	462 (34.0)	3 709 (28.4)	1.27	0.97	0.86, 1.10
Diclofenac	96 (7.1)	547 (4.2)	1.63	1.35	1.10, 1.67
Ibuprofen	42 (3.1)	446 (3.4)	0.91	0.85	0.62, 1.15
Naproxen	12 (0.88)	108 (0.83)	1.06	0.99	0.56, 1.75
Other traditional NSAIDs	38 (2.8)	262 (2.0)	1.36	1.10	0.79, 1.51
Cox-2 inhibitors	11 (0.81)	116 (0.89)	0.92	0.77	0.42, 1.39
Acetylsalicylic acid	319 (23.5)	2 656 (20.3)	1.18	0.88	0.77, 1.01

*Adjusted for gender, comorbidities, prescription of antibiotics, H₂-receptor antagonists, proton pump inhibitors and oral steroids.

Table 4

Crude and adjusted odds ratios (RR) of CDAD associated with NSAID exposure in the 90 days prior to the index date in non-hospitalized patients

NSAIDS exposure in the 90 days prior to the index date	Cases	Controls	Crude RR	Adjusted* RR	95% CI
Any traditional NSAID	303 (32.6)	2 284 (22.3)	1.43	1.04	0.90, 1.20
Diclofenac	66 (7.1)	351 (3.8)	1.80	1.43	1.11, 1.84
Ibuprofen	26 (2.8)	302 (3.3)	0.87	0.80	0.54, 1.18
Naproxen	10 (1.1)	69 (0.7)	1.40	1.12	0.60, 2.10
Other traditional NSAIDs	29 (3.1)	180 (1.9)	1.54	1.13	0.78, 1.64
Cox-2 inhibitors	10 (1.1)	73 (0.8)	1.33	1.03	0.55, 1.92
Acetylsalicylic acid	196 (21.1)	1 569 (16.9)	1.28	0.91	0.77, 1.08

*Adjusted for gender, comorbidities, prescription of antibiotics, H₂-receptor antagonists, proton pump inhibitors and oral steroids.

analysis to non-hospitalized patients. No association was found between the use of any other NSAIDs and the risk of CDAD.

The results of this study differ from those of Dial *et al.*, who found all NSAIDs combined to be associated with CDAD (adjusted RR 1.3, 95% CI 1.2, 1.5) [2]. This difference is likely explained by the different case definition, which for Dial *et al.* only included CDAD clinical diagnoses and toxin positive assays. The inclusion of additional cases who received a prescription of vancomycin likely reduced exposure misclassification and increased statistical power over the previous study. Furthermore, the previous work did not include subgroups for the analysis of NSAID use so the result in that study might also have been driven by an association between diclofenac and CDAD.

There are some key strengths to this study. It is set in the well validated GPRD and occurs in a broad population sample giving it the power to detect rare exposures and diseases. Furthermore, these results can likely be generalized to the United Kingdom general population, in so far as they are under treatment by a general practitioner. In order to reduce any bias due to trends over time, calendar time matching was used in the study design. Finally, confounding by indication was unlikely as CDAD was an unexpected adverse outcome and not an expected consequence of treatment.

However, this study also has known limitations. Confounding could have occurred despite a broad list of covariates as it is possible that there is an unknown confounding factor we did not include. There is also some concern that gastro-intestinal bleeding may be a variable in the causal pathway between NSAIDs and CDAD rather than a confounder. However, when gastro-intestinal bleeding was removed from the logistic regression model, the association between diclofenac and CDAD was not significantly altered making it unlikely to be a key mediator of this association.

Misclassification is possible as, in order to ascertain cases fully, three separate definitions were used as endpoints: physician diagnosis of CDAD, CDAD toxin positive assay, or prescription of vancomycin (for which the only indication is CDAD) [13]. Due to lack of power a sensitivity analysis comparing these case definitions was not feasible. If one of these case definitions was less specific than the others then this could have introduced a bias towards the null (which would have led to an underestimation of the strength of these associations). Another potential source of misclassification is that over the counter NSAIDs cannot be adjusted for, and therefore some medications, like aspirin, may have a fair degree of exposure misclassification [15]. However, since CDAD is a rare outcome disease in the GPRD, this misclassification of exposure should be

non-differential and result in an underestimation of the actual effect [16]. Furthermore, we did not assess any possible effect measure modification by gender, nor did we match on gender. This does create the possibility of residual confounding if gender is acting as an effect measure modifier for the association between NSAIDs and CDAD [17]. Similarly, we adjusted for age as a covariate in the model and age misspecification may also have led to some residual confounding.

Finally, the GPRD has limited information on hospitalizations as it relies on the hospital reporting back to the general practitioner. The concern that this could lead to differential ascertainment of cases was addressed by examining non-hospitalized patients in a sensitivity analysis. In this analysis, diclofenac remained the only NSAID significantly associated with CDAD and the estimate was comparable with that of the study.

In conclusion, no association was found between the use of any NSAID and the risk of developing CDAD. However, an association does exist between current diclofenac use and CDAD, regardless of previous hospitalization status. This finding is consistent with previous case reports identifying diclofenac as being linked to CDAD. As this is the first study to assess the risk of CDAD with regards to NSAID use using a population-based approach, continued study and replication of these associations are needed to better understand this possible risk factor for developing CDAD.

Competing Interests

There are no competing interests to declare.

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