

Anti-inflammatory drugs and variceal bleeding: a case-control study

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Abstract

Background—Non-steroidal anti-inflammatory drugs (NSAIDs) can have severe gastrointestinal effects and cause peptic ulcers to bleed. Acute bleeding from oesophageal varices is a major complication of cirrhosis of the liver.

Aims—To investigate the role, using a case-control study, of NSAIDs in first bleeding episodes associated with oesophageal or cardiac varices in cirrhotic patients.

Patients/Methods—A structured interview was conducted of 125 cirrhotic patients with bleeding mainly related to oesophageal varices and 75 cirrhotic controls with oesophageal varices who had never bled.

Results—Cirrhotic patients who were admitted for bleeding related to portal hypertension were more likely to have used NSAIDs during the week before the index day (31 of 125 (25%)) than the cirrhotic controls (eight of 75 (11%); odds ratio = 2.8, $p = 0.016$). Use of aspirin alone or combined with other NSAIDs was also more prevalent in the cases (21 of 125 (17%)) than in the controls (three of 75 (4%); odds ratio = 4.9, $p = 0.007$). Logistic regression analysis showed that NSAID use ($p = 0.022$, odds ratio = 2.9, 95% confidence interval = 1.8 to 4.7) and variceal size ($p < 0.001$, odds ratio = 4.0, 95% confidence interval = 1.4 to 11.5) were the only variables independently associated with the risk of bleeding.

Conclusions—Aspirin, used alone or combined with other NSAIDs, was associated with a first variceal bleeding episode in patients with cirrhosis. Given the life threatening nature of this complication, the possible benefit of this treatment should be weighed against the risk shown here. No firm conclusions could be drawn on non-aspirin NSAIDs used alone.

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Keywords: portal hypertension; non-steroidal anti-inflammatory drugs; variceal bleeding; aspirin; cirrhosis

A number of large case-control and cohort studies have incriminated non-steroidal anti-inflammatory drugs (NSAIDs) in gastrointestinal bleeding.¹⁻⁷ Patients who take aspirin or non-aspirin NSAIDs are about three times more likely to have serious gastrointestinal problems¹ and peptic ulcer bleeding⁶ than those who do not. The risk seems to be influenced by age, a previous history of gastrointestinal problems, the dose and type of NSAID, and concomitant consumption of alcohol, steroids, or a combination of aspirin

and non-aspirin NSAIDs.¹⁻³ The other adverse gastrointestinal effects of NSAIDs include non-specific ulceration of the small intestinal mucosa,⁸ which may account for bleeding,⁹ and strictures and protein-losing enteropathy.⁸ However, oesophageal lesions have not been conclusively linked to the use of NSAIDs in epidemiological studies.

Acute bleeding from oesophageal varices is a major complication of hepatic cirrhosis. Elevated portal blood flow and portal pressure¹⁰ are necessary for the appearance of gastro-oesophageal varices, while other factors such as the size of the varix, wall thickness, and transmural pressure tend to favour bleeding.¹⁰⁻¹¹ The role of NSAIDs in bleeding as the result of portal hypertension has not been evaluated, as cirrhotic patients are systematically excluded from case-control and cohort studies. In a recent study we observed that the use of aspirin was more prevalent in cirrhotic patients presenting with a first episode of variceal bleeding than in non-cirrhotic controls.¹²

This multicentre case-control study was carried out to compare anti-inflammatory drug use by cirrhotic patients admitted to hospital with a first bleeding episode associated with oesophageal or cardiac varices and in matched hospitalised cirrhotic control patients.

Methods

PATIENTS

All cirrhotic adults admitted to nine French hospitals between February 1995 and May 1996 with a first bleeding episode, defined as haematemesis, melaena, or bright red rectal bleeding related to portal hypertension were enrolled in this study. The source of bleeding was identified by endoscopy within 12 hours of admission. Patients were not included if emergency endoscopy was not performed or if it identified another source of bleeding not related to portal hypertension, such as reflux oesophagitis, gastric or duodenal ulcer, gastric carcinoma, or any intestinal lesion not related to portal hypertension. Patients were not included in cases of severe encephalopathy or death, even if their relatives were present at the time of admission, in order to avoid bias during collection of data on previous drug intake.

SELECTION OF CONTROLS

Each patient was matched, whenever possible, with one control of the same sex and age (to within five years), who was admitted for the first time to the same department within two weeks of admission of the case, with a history of

Abbreviation used in this paper: NSAID, non-steroidal anti-inflammatory drug.

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Table 1 Baseline characteristics of cases and controls, habitus, and intake of non-NSAID drugs during the week preceding admission

Characteristics	Cases n=125	Controls n=75
Age (mean (SD))	57 (11)	55 (10)
Gender (No of men)	94 (75%)	57 (76%)
Alcoholic cirrhosis	110 (88%)	68 (91%)
Child-Pugh class* (No of patients)		
A	24 (19%)	9 (12%)
B	49 (39%)	31 (41%)
C	52 (42%)	35 (47%)
Variceal size† (No of patients)		
1	6 (5%)	32 (43%)
2	70 (57%)	30 (40%)
3	47 (38%)	13 (17%)
Ascites‡ (No of patients)		
1	59 (47%)	21 (28%)
2	31 (25%)	20 (27%)
3	35 (28%)	34 (45%)
Diabetes mellitus (No of patients)	22 (18%)	12 (16%)
Smoking (No of patients)	70 (57%)	43 (57%)
Alcohol consumption (No of patients)	99 (80%)	61 (81%)
β blocker use (No of patients)	22 (18%)	7 (9%)
Acetaminophen use (No of patients)	24 (19%)	11 (15%)

*Class A denotes good hepatic function, class B intermediate hepatic function, and class C poor hepatic function.

†Two data missing; grade 1 corresponds to varices which flatten after insufflation, and grade 2 to moderate varices remaining after insufflation, and grade 3 to large varices.

‡Grade 1 corresponds to absence of ascites, grade 2 to moderate and grade 3 to severe ascites. NSAID, non-steroidal anti-inflammatory drug.

cirrhosis. Endoscopy was systematically performed to identify oesophageal or cardiac varices. Patients were not included as controls if they had current or previous gastrointestinal bleeding, or previous peptic ulceration or perforation.

DATA COLLECTION

The patients and controls were subjected to the same structured interview by a specially trained doctor. A three page questionnaire was used to obtain details of all drug intake, whether prescribed or self administered, during the week preceding either the bleeding episode (patients) or admission (controls), together with various other features including smoking habits, alcohol consumption, the presence of diabetes, previous bleeding episodes, and the cause of the cirrhosis. The part of the interview on drug intake started with questions on headache, arthralgia, myalgia, fever, or any pain that might have warranted the use of aspirin, non-aspirin NSAIDs, or any other drug. Patients were then asked to recall the trade names in a list of the most popular aspirin and non-aspirin NSAID-containing medications. The precise time of consumption was recorded for each drug, together with the dose and route of administration.

STATISTICAL ANALYSIS

Baseline characteristics were compared by using Fisher's exact test for proportions and the Mann-Whitney non-parametric test for means, both at the 5% significance level. The prevalence of the exposure variable, defined as aspirin and/or non-aspirin NSAID use, was compared between cases and controls by using Fisher's exact test. Potentially confounding factors, namely age, gender, Child-Pugh class,¹³ variceal size, β blocker use, and paracetamol intake, were taken into account in a stratified analysis using the Mantel-Haenzel χ^2 test and multivariate logistic regression analysis. The link between the exposure variables and variceal bleeding is

expressed as the odds ratio and 95% confidence interval. Computations were performed using the SAS package version 6.11 for Windows. The study protocol was approved by the local ethics committee.

Results

During the study period, 187 consecutive cirrhotic patients were admitted because of bleeding related to oesophageal or cardiac varices confirmed by emergency endoscopy. In 125 cases, it was the first episode of bleeding, and these patients were enrolled in the study. During the same period, 128 cirrhotic patients with no previous or current variceal bleeding or previous hospital admission were admitted: endoscopy showed no oesophageal or cardiac varices in 53 of these patients. Therefore only 75 controls with varices could be enrolled.

Table 1 gives descriptive statistics for the cases and controls. No significant differences were observed between the two groups in terms of age ($p = 0.20$), gender ($p = 1$), the Child-Pugh class ($p = 0.43$), serum albumin ($p = 0.62$), prothrombin time ($p = 0.22$), degree of encephalopathy ($p = 0.26$), presence of diabetes mellitus ($p = 0.85$), alcohol ($p = 0.85$) and tobacco consumption ($p = 1$), and recent use of β blockers ($p = 0.15$) and paracetamol ($p = 0.45$). At endoscopy, oesophageal varices were found to be significantly larger in the patients than in the controls ($p < 0.001$, Fisher's exact test). Bleeders using NSAIDs did not differ from those not using NSAIDs ($p = 1$). Ascites was more severe in the control group ($p = 0.004$) and was the main cause of hospital admission in cirrhotic patients without bleeding.

More patients than controls had used NSAIDs during the week before the index day (31 of 125 (25%) *v* eight of 75 (11%); odds ratio = 2.8, $p = 0.016$). Use of aspirin alone or combined with non-aspirin NSAIDs was also more prevalent in the cases than the controls (21 of 125 (17%) *v* three of 75 (4%); odds ratio = 4.9, $p = 0.0066$).

The following variables were introduced in a logistic regression model: overall NSAID use, age, gender, Child-Pugh class, ascites, variceal size, and recent use of β blockers. When a backward elimination procedure was applied, only two of these variables reached the level of significance: overall NSAID use ($p = 0.022$; odds ratio = 2.9; 95% confidence interval = 1.8 to 4.7) and variceal size ($p < 0.001$; odds ratio = 4.0; 95% confidence interval = 1.4 to 11.5; table 2). The goodness of fit, χ^2 , for this model was 41.0 ($p < 0.001$). Using the same model, on

Table 2 Prevalence of NSAID use in cases and controls by variceal size at endoscopy

Variceal size	Cases (%) n=125	Controls (%) n=75	Odds ratio
Grade 1	17	13	1.4
Grade 2	26	13	2.3
Grade 3	23	0	∞

When a backward logistic regression procedure was applied, both variceal size (odds ratio = 4.0; 95% confidence interval = 1.4 to 11.5; $p < 0.001$) and adjusted effect of NSAID use (odds ratio = 2.9; 95% confidence interval = 1.8 to 4.7; $p = 0.022$) reached the level of significance.

NSAID, non-steroidal anti-inflammatory drug.

introduction of the exposure variable (aspirin alone or combined with non-aspirin NSAIDs—that is, excluding those patients who took only non-aspirin NSAIDs), only two variables were significant, aspirin alone or combined with non-aspirin NSAIDs ($p = 0.020$; odds ratio = 4.7; 95% confidence interval = 1.3 to 17.3) and variceal size ($p < 0.001$; odds ratio = 3.9; 95% confidence interval = 2.4 to 6.6). The goodness of fit, χ^2 , for this model was 42.3 ($p < 0.001$). In patients with grade 1 oesophageal varices, neither NSAID use (odds ratio = 1.4, $p = 0.78$) nor use of aspirin alone (odds ratio = 6.2, $p = 0.22$) was associated with an increased risk of bleeding.

Among the 125 cases, there were no differences between NSAID users and non-users in terms of the site of bleeding (oesophageal varices in 30 of 31 users (97%) and 91 of 94 non-users (97%); cardiac varices in one (3%) and three (3%) respectively; none bled from gastric varices; severe portal hypertensive gastropathy was observed in one non-user). Similarly there were also no differences between NSAID users and non-users in terms of the presence of non-bleeding lesions which were not considered as the cause of bleeding at emergency endoscopy: oesophageal erosions or ulcers (two of 31 (6%) of NSAID users, and six of 94 (6%) of non-users) or gastric and/or duodenal ulcers or erosions (four (13%) and 14 (15%) in users and non-users respectively). NSAIDs were used by patients with bleeding for the following main reasons: headache in eight cases, arthralgia in six, myalgia in three, flu-like illness in three, coronary heart disease in four, various pains in three, and other causes in four. Among the 21 patients who used aspirin, five took less than 300 mg per day and 16 took 300 mg or more per day. Aspirin was usually taken in tablet form. Five patients took buffered tablets and none used enteric-coated preparations.

Discussion

This case-control study suggests that cirrhotic patients who use NSAIDs are about three times more likely to have a first variceal bleeding episode than cirrhotic patients who do not. The risk appeared to be due mainly to aspirin, alone or combined with other NSAIDs, only in patients with grade 2 or 3 varices. No conclusions on exclusively non-aspirin NSAID use or severity of bleeding related to NSAID use could be drawn. To avoid bias related to misinterpretation of endoscopic findings, we chose to enrol patients bleeding from oesophageal or cardiac varices. Bleeding from isolated gastric varices was never observed during the study period. Non-bleeding isolated gastric varices or portal hypertensive gastropathy was not systematically recorded in either patients or controls.

Aspirin is usually self administered in France, and non-aspirin NSAIDs were not available over the counter at the time of the study. There is no clear reason for the low prescription rate of non-aspirin NSAIDs, although they may have adverse renal effects in cirrho-

sis,¹⁴ and their known gastrointestinal toxicity in non-cirrhotics may also have reduced their prescription.

Several potential biases must be taken into account in this study. Cirrhotic patients with a previous history of bleeding were not enrolled as they may have avoided NSAIDs. It was difficult to recruit age- and sex-matched cirrhotic patients found to have oesophageal or gastric varices at endoscopy who reported never having bled previously. This was not surprising, as the usual reason for the first hospital admission of patients with medium or large varices is variceal bleeding. As a consequence, variceal size differed between cases and controls, and logistic regression analysis showed that variceal size and NSAIDs were independently associated with bleeding.

This case-control study was unlikely to have suffered from the classical bias related to the prior beliefs of the doctors about NSAIDs and disease, as the interviews with both patients and controls were conducted by the same doctor in each centre using a structured questionnaire. The investigator was not blinded to the subjects' status (case or control), as all patients with gastrointestinal bleeding, whatever the cause, are admitted to a specialised intensive care unit in each of the participating centres. However, the use of another common non-prescription analgesic, paracetamol, was comparable in the two groups, arguing against an overestimation of drug intake in the cases. The link between NSAIDs and bleeding was unchanged after controlling for confounding variables by logistic regression. The severity of the liver disease (Child's class) was comparable in the cases and controls and did not affect the risk of bleeding in the logistic regression model. Patients with confusion related to encephalopathy were not included in order to minimise recall bias, although we cannot exclude the possibility that subclinical encephalopathy was present. However, the same prevalence of paracetamol intake in the two groups argues against such recall bias. The prevalence of recent alcohol intake was also similar in the two groups. The first variceal bleeding episode is easily predicted by variceal size,¹⁵ and in this study, logistic regression analysis confirmed that variceal size was independently associated with bleeding. The prevalence of NSAID use by the cirrhotic patients who bled was lower than the 34% that we observed in a previous study,¹² but similar to the 19% reported by Wilcox *et al.*¹⁶ NSAID use by the cirrhotic controls (11%) compared well with that (12%) in non-cirrhotic controls in a previous study.¹²

Precisely how aspirin induces variceal bleeding cannot be deduced from our results. Rupture of oesophageal varices is mainly due to raised variceal pressure.¹⁰ Oesophagitis is controversial as a cause of variceal bleeding. Oesophageal transection has been used as a salvage procedure, and careful histological analysis of transection rings provided no evidence of oesophagitis,^{17, 18} although NSAID use in the few cases reported was not mentioned. However, large subepithelial blood

filled channels are frequent in the portal hypertensive oesophagus and may indicate increased variceal fragility.¹⁸ NSAID use is not a risk factor for ulcerative reflux oesophagitis in non-cirrhotics.¹⁹ Many reports have shown a link between NSAID use and the emergence of oesophageal ulcers, benign strictures, and bleeding,²⁰⁻²⁶ although some authors have suggested that non-aspirin NSAIDs may have protective properties in these respects.²⁷⁻²⁸

NSAID induced gastric mucosal damage probably results from a complex mechanism. Local mucosal injury and inhibition of cyclooxygenase type I activity lead to a reduction in mucosal defences, restricted mucosal blood flow,²⁹ and gastric erosions, which may facilitate cardiac or fundic variceal rupture. However, the prevalence of non-bleeding ulcers and erosions in this study was comparable in NSAID users and non-users. Another possible explanation for the increased risk of bleeding is the inhibitory effect of aspirin on platelet aggregation,³⁰ added to the platelet adhesion defect which may already be present in patients with cirrhosis.³¹

In conclusion, aspirin, alone or combined with non-aspirin NSAIDs, was associated with a first variceal bleeding episode in patients with cirrhosis. Given the life threatening nature of this complication, the possible benefit of the drug must be weighed against the risk shown here. No firm conclusions could be drawn on the use of non-aspirin NSAIDs alone. Paracetamol remains the preferred over the counter analgesic and antipyretic drug, as it carries the lowest risk of adverse reactions, even in alcoholics, when used at the recommended doses.³²

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