

NITROVASODILATORS, LOW-DOSE ASPIRIN, OTHER NONSTEROIDAL ANTIINFLAMMATORY DRUGS, AND THE RISK OF UPPER GASTROINTESTINAL BLEEDING

ANGEL LANAS, M.D., EDUARDO BAJADOR, M.D., PEDRO SERRANO, M.D., JAVIER FUENTES, M.D., SOFÍA CARREÑO, M.D., JESUSA GUARDIA, M.D., MERCEDES SANZ, M.D., MIGUEL MONTORO, M.D., AND RICARDO SÁINZ, M.D.

ABSTRACT

Background The relation between medications that release nitric oxide, such as nitroglycerin and other nitrovasodilators, and upper gastrointestinal bleeding is uncertain. In animals, these medications reduce the gastric damage induced by nonsteroidal antiinflammatory drugs. Nitric oxide, however, inhibits platelet aggregation and may contribute to bleeding from an ulcer.

Methods We performed a case-control study to determine the risk of bleeding in patients taking nitrovasodilators, low-dose aspirin, or other nonsteroidal antiinflammatory drugs. The case group was made up of 1122 consecutive patients admitted to one of four hospitals with bleeding from a peptic lesion. The 2231 control subjects were 1109 patients hospitalized for other reasons and 1122 outpatients from the same geographic area.

Results In the week before admission, 520 (46.3 percent) of the patients with bleeding had taken a nonsteroidal antiinflammatory drug other than low-dose aspirin, 120 (10.7 percent) had taken low-dose aspirin (≤ 300 mg per day), 60 (5.3 percent) a nitrovasodilator, and 135 (12.0 percent) an antisecretory agent such as a histamine H_2 -receptor antagonist or a proton-pump inhibitor. In multivariate models that adjusted for age, sex, and clinical risk factors, the use of a nonsteroidal antiinflammatory drug other than low-dose aspirin was independently associated with an increased risk of bleeding from a peptic ulcer (odds ratio, 7.4; 95 percent confidence interval, 4.5 to 12.0), as was the use of low-dose aspirin alone (odds ratio, 2.4; 95 percent confidence interval, 1.8 to 3.3). The use of a nitrovasodilator was associated with a decreased risk of bleeding (odds ratio, 0.6; 95 percent confidence interval, 0.4 to 0.9), as was antisecretory therapy (odds ratio, 0.6; 95 percent confidence interval, 0.4 to 0.8). In patients taking any type of nonsteroidal antiinflammatory drug, the use of a nitrovasodilator or antisecretory therapy was independently associated with a decreased risk of bleeding.

Conclusions The use of nitrovasodilator drugs is independently associated with a decreased risk of upper gastrointestinal bleeding. (N Engl J Med 2000; 343:834-9.)

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NONSTEROIDAL antiinflammatory drugs, including low-dose aspirin, induce gastrointestinal complications.¹⁻³ Although new and potentially safer nonsteroidal antiinflammatory drugs (such as cyclooxygenase-2 inhibitors) are now in use,⁴ it is uncertain whether these new drugs will reduce the number of patients hospitalized with gastrointestinal bleeding. Over-the-counter nonsteroidal antiinflammatory drugs, especially aspirin, are the drugs most frequently associated with bleeding,⁵ and the number of people taking low-dose aspirin is increasing.³

Nonsteroidal antiinflammatory drugs that release nitric oxide are under investigation.^{6,7} Nitric oxide increases blood flow in the gastric mucosa and inhibits the adherence of leukocytes to the endothelium within the gastrointestinal microcirculation. This mechanism may be important in the initiation of mucosal damage by nonsteroidal antiinflammatory drugs in animals⁸ as well as in humans.⁹ In rats, oral or parenteral administration of drugs that release nitric oxide, including transdermal nitroglycerin, prevents gastric damage and accelerates the healing of ulcers.¹⁰⁻¹² However, the mechanisms by which nonsteroidal antiinflammatory drugs induce acute mucosal damage in animals are not necessarily related to those underlying the chronic damage or complications that may occur in humans. Furthermore, inhibition of platelet aggregation by nonsteroidal antiinflammatory drugs may be involved in gastrointestinal bleeding in humans.¹³

Drugs that release nitric oxide inhibit platelet aggregation and may promote bleeding in patients taking these drugs.¹⁴ In clinical practice, patients with vascular occlusive diseases are often treated with nitrovasodilators. Since many of these patients are also treated with low-dose aspirin or other nonsteroidal antiinflammatory drugs, the potential effect of the nitric oxide generated by the nitrovasodilators on the risk of gastrointestinal bleeding is important. In a preliminary, retrospective study, we found that nitrovasodilators may reduce the risk of upper gastrointestinal bleeding associated with the use of low-dose

From the Service of Digestive Diseases, University Hospital (A.L., P.S., S.C., R.S.) and the Service of Digestive Diseases, Hospital Miguel Servet (E.B., J.F), Zaragoza; the Service of Digestive Diseases, Hospital San Jorge, Huesca (J.G., M.M.); and the Service of Digestive Diseases, Hospital San Millán, Logroño (M.S.) — all in Spain. Address reprint requests to Dr. Lanas at the Servicio de Aparato Digestivo, Hospital Clínico Universitario, 50009 Zaragoza, Spain, or at alanas@posta.unizar.es.

aspirin.¹⁵ We now report the results of a case-control study in which we sought to determine the risk of upper gastrointestinal bleeding from peptic lesions that was associated with the use of low-dose prophylactic aspirin, other nonsteroidal antiinflammatory drugs, nitrovasodilators, or various combinations of these drugs.

METHODS

Study Population

In this prospective, case-control study, patients with bleeding were recruited from among the patients admitted consecutively to four general hospitals in Spain (University Hospital and Hospital Miguel Servet, Zaragoza; Hospital San Jorge, Huesca; and Hospital San Millán, Logroño) between November 1995 and February 1998. Patients were eligible if they had acute gastrointestinal bleeding, defined as hematemesis or melena that was confirmed by hospital records, accompanied by evidence that peptic lesions (including ulcers, erosions, and acute mucosal lesions) of the upper gastrointestinal tract were the cause of the bleeding episode, as documented by endoscopy performed within the first 24 hours after hospital admission.

For most of the patients, two control subjects (one patient from the participating hospital and one outpatient from the community) were recruited. All the patients and controls underwent a structured interview; each control subject was interviewed by the same investigator who had interviewed the patient with whom he or she was matched. The controls were chosen to achieve frequency matching with the patients according to sex and age (± 5 years). Controls from the hospital were eligible if they had been admitted with any primary diagnosis that was neither an indication for nor a known complication of treatment with nonsteroidal antiinflammatory drugs. Therefore, potential controls were excluded if the main reason for admission was painful skeletal-muscle disease, acute myocardial infarction, acute peptic ulceration, or gastrointestinal bleeding or perforation. Controls from the community were drawn from among the outpatients seen by family practitioners in the same geographic area as the hospitals and were enrolled according to the same criteria as the controls from the hospitals. The index day for the outpatient controls was the day of the interview.

Clinical information for patients and inpatient controls was obtained from records made during hospitalization. Clinical information for outpatient controls was obtained from records from family practitioners, if available. The presence or absence of the following clinical variables was assessed: a history of upper gastrointestinal bleeding due to peptic lesions (ulcers and acute mucosal damage) as confirmed by endoscopic examination; a history of either gastric or duodenal ulcer as confirmed by endoscopic examination; rheumatic disease, including a clinical diagnosis of osteoarthritis or any other type of arthritis; ischemic heart disease, including a clinical diagnosis of angina (defined as typical chest pain and a transient ST-segment elevation or depression of 1 mm or more), a previous myocardial infarction, or previous coronary revascularization; cerebrovascular disease, defined as a previous stroke or transient ischemic attack as confirmed by medical records; liver disease, including a clinical diagnosis of hepatitis or cirrhosis; alcohol use, defined as the consumption of an alcoholic beverage at least three times per week; and current smoking, defined as the daily smoking of any number of cigarettes or cigars. A variable for the hospital where the patient or control was recruited was also created; outpatient controls were ascribed to the hospital in their geographic area for this variable.

Treatment with any nonsteroidal antiinflammatory drug was defined as the use of a drug of this class at any time during the seven days before hospital admission or the day of the interview (for outpatient controls). Treatment with low-dose aspirin was defined as the continuous use of up to 300 mg of aspirin per day for prophylaxis against vascular occlusive diseases. Similarly, treatment with

nitrovasodilator drugs was defined as continuous, daily use of any of these drugs either orally (glyceryl trinitrate, isosorbide dinitrate, or isosorbide mononitrate) or transdermally (any dose of nitroglycerin) for prophylaxis against vascular occlusive diseases. Antisecretory therapy was defined as treatment with a histamine H₂-receptor antagonist (ranitidine at a dose of 150 to 300 mg per day or famotidine at a dose of 20 to 40 mg per day) or a proton-pump inhibitor (omeprazole at a dose of 20 mg per day) for more than seven days before hospital admission or the day of the interview (for outpatient controls). Treatment with antacids included use of almagate at various doses (1 to 4 g per day). Data on the presence or absence of *Helicobacter pylori* infection were not recorded.

The study was approved by the ethics committees of all the participating hospitals, and as required by the ethics committees, all the patients and controls gave witnessed, oral informed consent. Of all the eligible patients and controls, 73 (16 patients and 57 controls) declined to participate.

Statistical Analysis

The results are expressed as means \pm SD. Bivariate analysis of all the variables pertaining to medical history, drug use, smoking status, and alcohol intake was performed by the chi-square test and by Student's t-test for either equal or unequal variances, as appropriate. To adjust for possible confounding factors, unconditional logistic-regression analysis was carried out (SPSS software, version 6.0, SPSS, Chicago), and the influence of various risk factors on upper gastrointestinal bleeding, as the dependent variable, was quantified.

A logistic-regression model was constructed by a stepwise, forward conditional method. A variable was entered into the model if the significance level was less than 0.05 and was removed if the significance level was greater than 0.10. Sex, age, and the hospital variables were the first variables entered into the model. Age was not categorized and was introduced as a continuous variable. Categorical variables included in the models were coded as dummy variables. Because the effects of other nonsteroidal antiinflammatory drugs may mask those of low-dose aspirin, we created a specific variable for the use of low-dose aspirin. Other variables included the use of different types of nonsteroidal antiinflammatory drugs or combinations of these drugs (nonsteroidal antiinflammatory drugs other than any dose of aspirin, aspirin at any dose, and nonsteroidal antiinflammatory drugs other than low-dose aspirin). Due to the interdependency of some variables in clinical practice, variables pertaining to cardiovascular disease and cerebrovascular disease were introduced into the models if the use of low-dose aspirin and the use of nitrovasodilator drugs had already been entered into the models; in the same way, the variable pertaining to the use of antisecretory therapy was introduced if a history of ulcer had already been entered.

Odds ratios and their 95 percent confidence intervals are reported. All reported P values are two-sided. On the basis of the results of our pilot study, we estimated that a study population comprising 1100 patients with bleeding and their controls would have a power of 80 percent to detect differences of 2 percent in the risk of bleeding according to the use or nonuse of low-dose aspirin or nitrovasodilator drugs. Smaller differences would probably be detected with the use of multivariate analysis and with a greater number of controls.

RESULTS

Characteristics of the Patients and Controls

A total of 1122 consecutive patients who were hospitalized in one of the four participating centers were enrolled. A total of 2231 controls from either the same hospitals (1109 subjects) or the same geographic areas (1122 subjects) were also enrolled. Table 1 shows the demographic and clinical characteristics of the patients and the controls. A history of

upper gastrointestinal bleeding, a history of ulcer, or the presence of rheumatic disease, cardiovascular disease, or cerebrovascular disease was found significantly more frequently in the patients than in the controls (Table 1).

The cause of the current bleeding episode was identified as a duodenal ulcer in 482 of the patients (43.0 percent), a gastric ulcer in 332 (29.6 percent), an acute gastroduodenal mucosal lesion in 222 (19.8 percent), and esophagitis in 86 (7.7 percent). Stig-

mata of bleeding were found in 382 patients (34.1 percent [7.5 percent with active bleeding, 7.5 percent with a visible vessel, and 19.1 percent with an adherent clot]).

Medications Used by the Patients and Controls

Of the 1122 patients, 640 (57 percent) had taken at least one nonsteroidal antiinflammatory drug of any type (including low-dose aspirin alone) during the week before hospital admission, as compared with only 435 (19.5 percent) of the 2231 controls ($P<0.001$). The nonsteroidal antiinflammatory drug most commonly taken by these 640 patients was aspirin at any dose (taken by 396 patients [61.9 percent]), either alone (323 patients [81.6 percent]) or in combination with other nonsteroidal antiinflammatory drugs (73 patients [18.4 percent]). Low-dose aspirin was also taken by a greater proportion of the patients than of the controls. Adjusted odds ratios indicated that nonsteroidal antiinflammatory drugs and low-dose aspirin were associated with an increased risk of upper gastrointestinal bleeding and that nitrovasodilator and antisecretory therapy were associated with a decreased risk of upper gastrointestinal bleeding (Table 2).

The effects of nitrovasodilators and antisecretory drugs are also presented in Tables 3 and 4. Nitrovasodilators were associated with a decreased risk of gastrointestinal bleeding in subjects taking nonsteroidal antiinflammatory drugs other than aspirin, aspirin (at any dose), or low-dose aspirin alone (Tables 3 and 4). The dose of low-dose aspirin used by the patients and controls was most often 200 mg per day (62.2 percent of the patients and controls who used low-

TABLE 1. CHARACTERISTICS OF THE STUDY POPULATION.

VARIABLE	PATIENTS (N=1122)	CONTROLS (N=2231)
Age — yr*	65.1±16.6	65.2±16.7
Sex — no. (%)		
Male	778 (69.3)	1544 (69.2)
Female	344 (30.7)	687 (30.8)
Current smoking — no. (%)	257 (22.9)	446 (20.0)
Alcohol use — no. (%)	283 (25.2)	541 (24.2)
History of upper gastrointestinal bleeding — no. (%)	264 (23.5)†	92 (4.1)
History of ulcer — no. (%)	401 (35.7)†	262 (11.7)
Rheumatic disease — no. (%)	268 (23.9)†	385 (17.3)
Cardiovascular disease — no. (%)	146 (13.0)‡	221 (9.9)
Cerebrovascular disease — no. (%)	158 (14.1)†	198 (8.9)
Liver disease — no. (%)	74 (6.6)	108 (4.8)

*Values are means ±SD.

† $P<0.001$ by the chi-square test for the comparison with the controls.

‡ $P=0.004$ by the chi-square test for the comparison with the controls.

TABLE 2. FREQUENCY OF USE OF MEDICATIONS AND ADJUSTED ODDS RATIOS FOR UPPER GASTROINTESTINAL BLEEDING ASSOCIATED WITH EACH TYPE OF MEDICATION, ACCORDING TO LOGISTIC-REGRESSION ANALYSIS.*

TYPE OF MEDICATION	PATIENTS (N=1122)	CONTROLS (N=2231)	ADJUSTED ODDS RATIO (95% CI)	P VALUE
Any nonsteroidal antiinflammatory drug other than low-dose aspirin†	520 (46.3)	229 (10.3)	7.4 (4.5–12.0)	<0.001
Low-dose aspirin alone	120 (10.7)	206 (9.2)	2.4 (1.8–3.3)	<0.001
Nitrovasodilator	60 (5.3)	137 (6.1)	0.6 (0.4–0.9)	0.03
Antisecretory medication	135 (12.0)	206 (9.2)	0.6 (0.4–0.8)	0.001

*Low-dose aspirin was defined as aspirin at a dose ≤ 300 mg per day. Variables included in the model were a history of upper gastrointestinal bleeding ($P<0.001$), a history of ulcer ($P<0.001$), cardiovascular disease ($P=0.01$), cerebrovascular disease ($P<0.001$), rheumatic disease ($P=0.002$), sex ($P=0.73$), age ($P=0.001$), and the hospital ($P=0.60$). Similar results were obtained when nitrovasodilator-drug use was introduced as a continuous variable according to dose (odds ratio, 0.6; 95 percent confidence interval, 0.4 to 0.9). CI denotes confidence interval.

†Twenty-eight patients and 14 controls took both nonsteroidal antiinflammatory drugs and low-dose aspirin and are included in this category.

TABLE 3. ADJUSTED ODDS RATIO FOR UPPER GASTROINTESTINAL BLEEDING ASSOCIATED WITH CLINICAL VARIABLES AND MEDICATION USE AMONG STUDY SUBJECTS TAKING NONSTEROIDAL ANTIINFLAMMATORY DRUGS OTHER THAN ASPIRIN AT ANY DOSE, ACCORDING TO LOGISTIC-REGRESSION ANALYSIS.*

FACTOR	PATIENTS (N=317)	CONTROLS (N=187)	ADJUSTED ODDS RATIO (95% CI)	P VALUE
History of gastrointestinal bleeding	37 (11.7)	6 (3.2)	3.7 (1.2–11)	0.01
History of ulcer	69 (21.8)	18 (9.6)	1.8 (0.9–3.6)	0.09
Aspirin at any dose	73 (23.0)	18 (9.6)	3.1 (1.7–5.9)	<0.001
Nitrovasodilator	11 (3.5)	11 (5.9)	0.3 (0.1–0.9)	0.04
Antisecretory medication	29 (9.1)	37 (19.8)	0.4 (0.2–0.7)	0.001

*Variables included in the model were cardiovascular disease (P=0.73), cerebrovascular disease (P<0.001), rheumatic disease (P=0.08), sex (P=0.10), age (P=0.01), and the hospital (P=0.26). CI denotes confidence interval.

TABLE 4. ADJUSTED ODDS RATIO FOR UPPER GASTROINTESTINAL BLEEDING ASSOCIATED WITH CLINICAL VARIABLES AND MEDICATION USE AMONG STUDY SUBJECTS TAKING ASPIRIN, ACCORDING TO LOGISTIC-REGRESSION ANALYSIS.*

FACTOR	ASPIRIN AT ANY DOSE		ADJUSTED ODDS RATIO (95% CI)	P VALUE	LOW-DOSE ASPIRIN		ADJUSTED ODDS RATIO (95% CI)	P VALUE
	PATIENTS (N=396)	CONTROLS (N=266)			PATIENTS (N=148)	CONTROLS (N=220)		
	no. (%)				no. (%)			
History of gastrointestinal bleeding	41 (10.4)	8 (3.0)	5.1 (2.0–13.1)	<0.001	20 (13.5)	5 (2.3)	6.5 (2.0–21.2)	0.001
History of ulcer	82 (20.7)	34 (12.8)	1.7 (1–2.9)	0.06	39 (26.4)	26 (11.8)	2.1 (1.0–4.1)	0.03
Nonsteroidal antiinflammatory drug other than aspirin	73 (18.4)	18 (6.8)	3.8 (2.1–6.9)	<0.001	28 (18.9)	14 (6.4)	3.8 (1.8–7.8)	<0.001
Nitrovasodilator	36 (9.1)	68 (25.6)	0.5 (0.2–0.8)	0.01	32 (21.6)	67 (30.5)	0.5 (0.2–0.9)	0.03
Antisecretory medication	30 (7.6)	42 (15.8)	0.3 (0.2–0.6)	0.001	19 (12.8)	39 (17.7)	0.4 (0.2–0.9)	0.04

*Low-dose aspirin was defined as aspirin at a dose ≤300 mg per day. Variables included in both models were cardiovascular disease, cerebrovascular disease, sex, age, and the hospital; rheumatic disease was included in the model for aspirin at any dose. CI denotes confidence interval.

dose aspirin), 150 mg per day (12.9 percent), or 125 mg per day (8.8 percent). Low-dose aspirin and nitrovasodilators were usually being taken on a long-term basis; 97 percent of the patients and controls who used low-dose aspirin and 99 percent of those who used nitrovasodilators had been taking the drug for longer than one month (and 91.6 percent and 94.4 percent, respectively, had been taking it for longer than three months) before hospital admission or the day of the interview (for the outpatient controls).

In the same way, 78.6 percent of those who were taking nitrovasodilators had been taking a standard dose of these drugs. The decrease in the risk of upper gastrointestinal bleeding associated with the use of nitrovasodilators was found for both transdermal preparations (nitroglycerin at a dose of 10 mg per day in

71.8 percent of those who used a transdermal preparation) and oral preparations (99 percent of which were isosorbide mononitrate at a standard dose of 40 to 60 mg per day) (Table 5). Among subjects who were taking nitrovasodilators, nitroglycerin and nitrates were being taken by 58.3 percent and 41.7 percent of the 60 patients, respectively, as compared with 64.2 percent and 35.8 percent of the 137 controls. A history of peptic ulcer or of upper gastrointestinal bleeding was a risk factor for upper gastrointestinal bleeding in patients taking any type of nonsteroidal antiinflammatory drug (Tables 2, 3, and 4).

Antisecretory therapy was associated with a decreased risk of bleeding in subjects using any type of nonsteroidal antiinflammatory drug (Tables 3 and 4). The association was found for both H₂-receptor an-

TABLE 5. ADJUSTED ODDS RATIO FOR UPPER GASTROINTESTINAL BLEEDING ASSOCIATED WITH VARIOUS TYPES OF NITROVASODILATORS AND ANTISECRETORY DRUGS, ACCORDING TO LOGISTIC-REGRESSION ANALYSIS.*

TYPE OF MEDICATION	OVERALL	NSAID OTHER	ASPIRIN AT ANY	LOW-DOSE
		THAN ASPIRIN AT ANY DOSE	DOSE	ASPIRIN ALONE
adjusted odds ratio (95% CI)				
Transdermal nitrovasodilator	0.5 (0.3–0.9)	0.2 (0.1–1.2)	0.7 (0.3–1.3)	0.7 (0.3–1.5)
Oral nitrovasodilator	0.5 (0.2–0.9)	0.5 (0.1–2.3)	0.5 (0.2–1.0)	0.5 (0.2–1.2)
Antacid	1.1 (0.6–1.9)	1.2 (0.2–5.9)	1.1 (0.2–4.7)	1.2 (0.2–5.9)
H ₂ -receptor antagonist	0.6 (0.4–0.8)	0.4 (0.2–0.9)	0.4 (0.2–0.9)	0.5 (0.2–1.2)
Omeprazole	0.6 (0.4–0.9)	0.2 (0.1–0.7)	0.2 (0.1–0.5)	0.2 (0.1–0.9)

*Variables included in the models were a history of gastrointestinal bleeding, a history of peptic ulcer, cardiovascular disease, cerebrovascular disease, type of nonsteroidal antiinflammatory drug use (where appropriate), sex, age, and the hospital. CI denotes confidence interval, and NSAID nonsteroidal antiinflammatory drug.

tagonists (taken by 8.3 percent of the patients and 6.1 percent of the controls) and proton-pump inhibitors (taken by 3.8 percent of the patients and 3.3 percent of the controls). The most commonly used proton-pump inhibitor was omeprazole (taken by 92.3 percent of those using a proton-pump inhibitor). The use of antacids (taken by 2.8 percent of the patients and 1.8 percent of the controls) was not associated with a decrease in the risk of upper gastrointestinal bleeding (Table 5).

The odds ratio for gastrointestinal bleeding in subjects taking aspirin (at any dose) for one month or less, as compared with patients who were not taking either aspirin or another nonsteroidal antiinflammatory drug, was 8.9 (95 percent confidence interval, 6.6 to 14.5); in those taking a nonsteroidal antiinflammatory drug other than aspirin (at any dose) for one month or less, the odds ratio was 7.6 (95 percent confidence interval, 5.8 to 9.2). The odds ratio for bleeding in subjects taking aspirin (at any dose) for more than one month was 2.8 (95 percent confidence interval, 1.6 to 4.0) and for those taking other nonsteroidal antiinflammatory drugs (at any dose) for more than one month it was 2.4 (95 percent confidence interval, 1.8 to 3.9). In addition, the odds ratio for bleeding in subjects taking the standard dose of any nonsteroidal antiinflammatory drug, as compared with those who were not taking aspirin or another nonsteroidal antiinflammatory drug, was 6.9 (95 percent confidence interval, 6.0 to 9.3), whereas the odds ratio in those taking a dose higher than the standard dose was 9.4 (95 percent confidence interval, 6.3 to 14.2), and in those taking a dose lower than the standard dose it was 1.6 (95 percent confidence interval, 1.1 to 2.1).

DISCUSSION

In this case-control study, we found that drugs that generate nitric oxide, when taken as organic ni-

trates or nitroglycerin, are independently associated with a decreased risk of upper gastrointestinal bleeding. This association was evident in patients taking nonsteroidal antiinflammatory drugs, including low-dose aspirin, and in patients taking either transdermal or oral preparations of these nitrovasodilators. Experimental studies have shown that drugs that release nitric oxide decrease the gastroduodenal mucosal damage induced by various nonsteroidal antiinflammatory drugs.^{6,7,10,11} Furthermore, when tested in rats, nonsteroidal antiinflammatory drugs that release nitric oxide while maintaining the antiinflammatory properties of the original drug induced little or no damage to the gastrointestinal mucosa and even accelerated the healing of acetic acid-induced gastric ulcers.¹² An aspirin derivative that releases nitric oxide has been developed.¹⁶ Endoscopic studies have shown that this type of drug may induce less damage to the gastroduodenal mucosa than classic nonsteroidal antiinflammatory drugs.¹⁷ However, the incidence of chronic lesions or complications is uncertain. For example, in endoscopic studies, enteric-coated or buffered aspirin induced little gastroduodenal damage,¹⁸ but plain, enteric-coated, and buffered aspirin carried similar risks of serious upper gastrointestinal bleeding.¹⁹ Furthermore, nitrovasodilators inhibit platelet aggregation,¹⁴ which contributes to the gastrointestinal bleeding due to either aspirin or other nonsteroidal antiinflammatory drugs.^{13,20} Therefore, the use of agents that release nitric oxide may harm patients with gastroduodenal lesions.

We also found that treatment with antisecretory drugs was independently associated with a decreased risk of upper gastrointestinal bleeding. This association was present in all the groups of subjects analyzed, including those taking low-dose aspirin. This finding contrasts with the results of a study that found that the use of antisecretory drugs increased the risk

of bleeding in patients taking nonsteroidal antiinflammatory drugs.²¹ Although the difference in the type of study (a case-control design in our current study and a cohort analysis in the study by Singh et al.²¹) may explain the disparate results, it is possible that the main difference between the two studies is in the types of antisecretory agents used, which were omeprazole and H₂-receptor antagonists (ranitidine or famotidine) in the current investigation and mainly antacids and cimetidine in the cohort study. The ability of the latter two medications to decrease gastric acidity is much less than that of ranitidine or famotidine. In our study, antacids were not associated with a decreased risk of upper gastrointestinal bleeding. Both omeprazole and H₂-receptor antagonists afforded protection against bleeding; an even greater degree of protection was found with proton-pump inhibitors. Our data are consistent with the results of a recent study indicating that omeprazole afforded protection against new bleeding in patients with previous upper gastrointestinal bleeding who were taking nonsteroidal antiinflammatory drugs.²²

Finally, we identified several clinical factors (notably, a history of upper gastrointestinal bleeding, a history of ulcer, and the presence of cardiovascular and cerebrovascular disease) as independent risk factors for upper gastrointestinal bleeding. As in our previous studies,^{5,23} aspirin was the nonsteroidal antiinflammatory drug most commonly taken by patients with upper gastrointestinal complications. We also confirmed a previous finding that the risk of bleeding from a peptic ulcer in patients taking nonsteroidal antiinflammatory drugs was higher with high doses or short treatment periods (less than one month) than with low doses or long treatment periods.²⁴

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