Immunosuppressive agents are associated with peptic ulcer bleeding

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Abstract. Peptic ulcer bleeding can be fatal. Non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and immunosuppressive agents are administered for long-term usage. The present study assessed the association between peptic ulcer bleeding and administration of NSAIDs, corticosteroids and immunosuppressive agents. Furthermore, the efficacy of lowering the risk of peptic ulcer bleeding with proton pump inhibitors (PPI) and histamine 2 receptor antagonists (H2RA) was evaluated. Medical records were retrospectively analyzed for patients subjected to an upper gastrointestinal (GI) endoscopy performed at the National Hospital Organization Shimoshizu Hospital (Yotsukaido, Japan) from October 2014 to September 2015. During this period, a total of 1,023 patients underwent an upper GI endoscopy. A total of 1,023 patients, including 431 males (age, 68.1±12.9 years) and 592 females (age, 66.4±12.3 years), who had been administered NSAIDs, corticosteroids, immunosuppressive agents, PPIs and H2RAs, were respectively enrolled. Endoscopic findings of the patients were reviewed and their data were statistically analyzed. Logistic regression analysis was used to determine the odds ratio of peptic ulcer bleeding for each medication; immunosuppressive agents had an odds ratio of 5.83, which was larger than that for NSAIDs (4.77). The Wald test was applied to confirm the correlation between immunosuppressive agents and peptic ulcer bleeding. Furthermore, χ^2 tests were applied to the correlation between peptic ulcer bleeding and administration of PPIs or H2RAs. Immunosuppressive agents had the largest χ^2, and the P-value was 0.03. Administration of PPIs was significantly correlated with non-peptic ulcer bleeding (P=0.02); furthermore, a tendency toward non-peptic ulcer bleeding with administration of H2RA was indicated, but it was not statistically significant (P=0.12). In conclusion, immunosuppressive agents were correlated with peptic ulcer bleeding and PPIs were effective at lowering the risk of peptic ulcer bleeding.

Introduction

Peptic ulcers comprise gastric and duodenal ulcers. Complications of peptic ulcers include bleeding, perforation and obstruction (1). Bleeding is a major problem of peptic ulcers, as it is at times fatal (2). Peptic ulcer bleeding is diagnosed and treated by upper gastrointestinal (GI) endoscopy (3). Known causes of peptic ulcer bleeding are the long-term administration of non-steroidal anti-inflammatory drugs (NSAIDs), anti-platelet agents, anti-coagulants and infection with *Helicobacter pylori* (4).

NSAIDs are commonly used for rheumatic diseases and persistent pain due to orthopedic diseases (5,6). Rheumatic diseases have an autoimmune basis and affect connective tissue (6,7). This inflammation damages tissue and impairs the patient's quality of life (8,9). To suppress the autoimmune basis of the disease, corticosteroids and immunosuppressive agents are used (10-12). Tumor necrosis factor a blockers, biological modifiers, are also used to suppress the autoimmune response (13,14). It is well known that corticosteroids trigger peptic ulcer bleeding by making the gastric mucosa susceptible to ulceration by gastric acid (15-17). However, the correlation between immunosuppressive agents and upper GI bleeding has remained to be determined.

For the prevention of peptic ulcer bleeding, proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RAs) are used (18). PPIs and H2RAs increase the pH of gastric acid, prevent damage of the gastric mucosa and promote the healing of peptic ulcers (19,20). PPIs are superior to H2RAs in preventing peptic ulcer bleeding due to stress in patients in intensive care (21). However, the efficacy of the prevention of peptic ulcer bleeding has remained elusive in patients with long-term administration of PPIs or H2RAs.

In the present study, the association between peptic ulcer bleeding and administration of NSAIDs, corticosteroids and

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immunosuppressive agents was analyzed in patients with rheumatic or orthopedic diseases. Furthermore, the prevention of peptic ulcer bleeding by PPIs and H2RAs was evaluated.

Materials and methods

Ethics statement. The present study was approved by the National Hospital Organization Shimoshizu Hospital Ethics Committee (Yotsukaido, Japan). It was not considered a clinical trial, as the procedures were performed as part of a routine clinical practice. Written informed consent for inclusion in the study was waived. Patient records were anonymized and retrospectively analyzed. Written informed consent was obtained from all patients who were subjected to upper GI endoscopy.

Patients. Medical records were retrospectively analyzed for patients subjected to upper GI endoscopy performed at the National Hospital Organization Shimoshizu Hospital (Yotsukaido, Japan) from October 2014 to September 2015. During this period, a total of 1,023 patients underwent an upper GI endoscopy for the investigation of anemia, abdominal pain or tarry stool. In addition, certain patients underwent upper GI endoscopy for screening. The cohort comprised 431 males (age, 68.1±12.9 years) and 592 females (age, 66.4±12.3 years).

Study design. The 1,023 patents were analyzed with regard to administration of NSAIDs, corticosteroids, immunosuppressive agents, PPIs and H2RAs. Endoscopic findings were reviewed in the 1,023 patients; these data were analyzed statistically. For patients with bleeding from peptic ulcers, results of urea breath test and past history of peptic ulcers were reviewed. The urea breath test was performed to detect *Helicobacter pylori* infection and outsourced to LSI Medience Corp. (Tokyo, Japan).

Medication. The cohort of the present study had received immunosuppressive agents, including methotrexate and tacrolimus, as well as biological agents, including infliximab, etanercept, adalimumab and golimumab. Corticosteroids and immunosuppressive agents were used for rheumatic diseases, such as rheumatoid arthritis and systemic lupus erythematosus. NSAIDs were administered to patients with lumbar discopathy and deformation spondylosis. Table I shows the number and ratio of patients administered each type of drug.

Upper GI endoscopy. Patients were subjected to upper GI endoscopy for screening, or investigation of abdominal symptoms or anemia. The endoscopic devices used were the GIF-N260H, GIF-XP260NS, GIF-PG260, GIF-XQ260 and GIF-Q260 (Olympus, Tokyo, Japan). A gastric or duodenal ulcer was considered to be a peptic ulcer. Bleeding from a peptic ulcer was restricted to a spurting vessel, an oozing vessel, a visible vessel or a clot, according to the Forrest classification system (22). Table II shows the diagnosis of patients with peptic ulcer bleeding. Seventeen and two patients were diagnosed with bleeding from gastric and duodenal ulcers, respectively.

Statistical analysis. Logistic regression analysis was used to determine the odds ratio and 95% confidence interval of peptic ulcer bleeding for each medication. The Wald test was

Table I. Number of patients taking each medication.

Medication	Number of patients	Ratio, %
NSAIDs	19	1.85
Corticosteroids	92	8.99
Immunosuppressive agents	30	2.93
PPI	118	10.51
H2RA	30	2.93

NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor; H2RA, histamine type 2 receptor antagonist.

Table II. Diagnosis of upper gastrointestinal bleeding from peptic ulcers by endoscopy.

Peptic ulcer or non-peptic ulcer	Diagnosis	Number of patients
Peptic ulcer	Gastric ulcer	17
	Duodenal ulcer	2
Total		19

applied to analyze the statistical significance of the correlation of peptic ulcer bleeding and medication (23). Chi-square tests were applied to analyze the correlation between peptic ulcer bleeding and administration of PPIs or H2RAs. P<0.05 was considered to indicate a statistically significant difference. JMP 10.0.2 software (SAS Institute, Cary, CA, USA) was used for statistical analysis.

Results

Patient characteristics. Table III shows the characteristics of patients with bleeding from peptic ulcers. The patients had been subjected to monotreatment with NSAIDs, immunosuppressive agents or corticosteroid, but not their combination. Four patients were subjected to the urea breath test, one of which was positive and had a history of peptic ulcer.

Effect of the medication with regard to bleeding. To calculate the odds ratios for various medication types with regard to peptic ulcer bleeding, logistic regression analysis was used (Table IV). The odds ratio of immunosuppressive agents was 5.83, which was larger than that of NSAID (4.77). It was found that among the different medications, immunosuppressive agents had the strongest correlation with peptic ulcer bleeding.

Confirmation of the association between medication and bleeding. To confirm the association between immunosuppressive agents and peptic ulcer bleeding, the Wald test was applied (Table V). Immunosuppressive agents had the largest χ^2 result (4.98) and P=0.03 (Table V).

Proton-pump inhibitor and bleeding. To reveal the correlation between PPIs and peptic ulcer bleeding, a χ^2 test was

Table III. Characteristics of patients with bleeding from peptic ulcers.

Patient no.	Diagnosis	Gender	Age	Disease	NSAIDs	Immunosuppressive agents	Corticosteroids	History of peptic ulcers	*H. pylori*
1	GU	F	79	Lumbar discopathy	(+)	(-)	(-)	(-)	NA
2	GU	M	73	RA	(-)	(-)	(+)	(-)	NA
3	GU	M	73	RA	(-)	(-)	(+)	(-)	NA
4	GU	M	73	RA	(-)	(-)	(+)	(-)	NA
5	GU	F	66	(-)	(-)	(+)	(-)	(-)	NA
6	GU	F	67	RA	(-)	(+)	(-)	(-)	NA
7	GU	M	22	DMD	(-)	(-)	(-)	(-)	NA
8	GU	M	78	(-)	(-)	(-)	(-)	(-)	NA
9	GU	M	72	(-)	(-)	(-)	(-)	(+)	NA
10	GU	M	72	(-)	(-)	(-)	(-)	(+)	NA
11	GU	M	84	(-)	(-)	(-)	(-)	(-)	NA
12	GU	M	71	(-)	(-)	(-)	(-)	(-)	NA
13	GU	F	70	(-)	(-)	(-)	(-)	(-)	NA
14	GU	M	69	(-)	(-)	(-)	(-)	(+)	(+)
15	GU	F	84	(-)	(-)	(-)	(-)	(-)	NA
16	GU	F	87	(-)	(-)	(-)	(-)	(-)	NA
17	GU	F	70	(-)	(-)	(-)	(-)	(-)	(+)
18	DG	F	42	(-)	(-)	(-)	(-)	(-)	(-)
19	DG	F	42	(-)	(-)	(-)	(-)	(-)	(-)

NSAIDs, non-steroidal anti-inflammatory drugs; GU, gastric ulcer; DG, duodenal ulcer; M, male; F, female; RA, rheumatoid arthritis; DMD, Duchenne muscular dystrophy; NA, not analyzed; *H. pylori, Helicobacter pylori*.

Table IV. Logistic regression analysis of the relationship between medication and bleeding from peptic ulcers.

Medication	Odds ratio	95% CI
NSAIDs	4.77	0.25-26.88
Corticosteroids	2.77	0.62-9.09
Immunosuppressive agents	5.83	0.88-22.96

CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table V. Wald test of the association between medication and bleeding from peptic ulcers.

Medication	χ^2	P-value
NSAIDs	2.12	0.15
Corticosteroids	2.37	0.12
Immunosuppressive agents	4.98	0.03

NSAIDs, non-steroidal anti-inflammatory drugs.

applied (Table VI). Administration of PPIs was significantly correlated with non-peptic ulcer bleeding (P=0.02).

Table VI. Correlation between PPI intake and bleeding from peptic ulcers.

PPI intake	Peptic ulcer bleeding (P=0.02)		Total
	Negative, n (%)	Positive, n (%)	
Yes	892 (87.19)	13 (1.27)	905 (88.47%)
No	112 (10.95)	6 (0.59)	118 (11.53%)
Total	1,004 (98.14)	19 (1.86)	1,023 (100%)

PPI, proton pump inhibitor. P=0.02 compares PPI intake and no PPI treatment in peptic ulcer bleeding.

Histamine type 2 receptor antagonist and bleeding. To analyze the correlation between H2RAs and peptic ulcer bleeding, a χ^2 test was applied (Table VII). A tendency toward non-peptic ulcer bleeding with administration of H2Ras was identified; however, it was not statistically significant (P=0.12).

Discussion

Case reports and case series have documented the use of immunosuppressive agents to treat patients with peptic ulcers (24-26). However, studies assessing the possible association between the administration of immunosuppressive agents

Table VII. Correlation between H2RA intake and bleeding from peptic ulcers.

H2RA intake	Peptic ulcer bleeding (P=0.12)		Total
	Negative, n (%)	Positive, n (%)	
Yes	976 (95.41)	17 (1.66)	993 (97.07%)
No	28 (2.73)	2 (0.2)	30 (2.93%)
Total	1004 (98.14)	19 (1.86)	1023 (100%)

H2RA, histamine H2 receptor antagonist. P=0.12 compares H2RA intake and no H2RA treatment in peptic ulcer bleeding.

and peptic ulcer bleeding are currently lacking. To answer this question, the present case findings provided novel evidence that immunosuppressive agent use is significantly correlated with peptic ulcer bleeding. Although the mechanisms by which immunosuppressive agent use may be correlated with peptic ulcer bleeding is elusive, it is possible that these agents cause bleeding by inhibiting ulcer healing (26). The results of the present study are clinically important, as they are relevant to ensuring patient safety, with peptic ulcer bleeding being one reason for the discontinuation of immunosuppressive agents (27). Further studies with additional patients are therefore warranted to confirm these results.

NSAIDs and corticosteroids cause gastric and duodenal ulcers, and increase the risk of upper GI bleeding. In previous studies, NSAIDs and corticosteroids were rated to not pose any risk for peptic ulcer bleeding (28,29). In the present study, NSAIDs and corticosteroids showed no correlation with upper GI bleeding. The results of the present study are therefore consistent with those of previous ones. However, it is premature to conclude that NSAIDs and corticosteroids are less hazardous. One reason is that in the present study, the number of patients treated with NSAIDs and corticosteroids was relatively small. Peptic ulcer bleeding is still fatal in certain patients, such as the elderly (30). Precautions should be taken for patients treated with NSAIDs and/or corticosteroids to avoid upper GI bleeding.

PPIs are effective for reducing peptic ulcer bleeding (31). They are more effective at lowering the risk of upper GI peptic ulcer bleeding than H2RAs (32). In the present study, PPIs significantly lowered the risk of peptic ulcer bleeding. Therefore, the results of the present study were consistent with those of previous ones. PPIs are frequently used in combination with NSAIDs or corticosteroids to lower the risk of peptic ulcer bleeding (10,33). Likewise, PPIs may lower the risk of peptic ulcer bleeding associated with immunosuppressive agents. However, PPIs represent a risk factor for bleeding from the small intestine, hip fracture and cardiac events (34,35). It is therefore recommended that long-term use of PPIs is avoided (36). With this regard, H2RAs may be recommended for long-term administration to prevent peptic ulcer bleeding.

A major limitation is that the present study was based on a relatively small number of patients. This may explain why no correlation was found between NSAIDs, corticosteroids, immunosuppressive agents and upper GI bleeding. In future studies, a larger number of patients should be enrolled and studied.

In conclusion, the present study revealed that immunosuppressive agents were correlated with peptic ulcer bleeding. However, PPIs were effective at lowering the risk of peptic ulcer bleeding.

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