Risk Factors Associated with NSAID-Induced Upper Gastrointestinal Bleeding Resulting in Hospital Admissions: A Cross-Sectional, Retrospective, Case Series Analysis in Valencia, Spain

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ABSTRACT

Background: NSAIDs are a significant cause of drug-related hospital admissions and deaths. The therapeutic effects of NSAIDs have been associated with the risk for developing adverse events, mainly in the gastrointestinal tract.

Objectives: The focus of this study was to identify the most common risk factors associated with NSAID-induced upper gastrointestinal bleeding (UGIB) resulting in hospital admissions. A secondary end point was the relationship between use of gastroprotective treatment and relevant risk factors to NSAID-induced UGIB in the selected population.

Methods: This study was a cross-sectional, retrospective, case-series analysis of NSAID-induced UGIB resulting in hospital admission to the Requena General Hospital, Valencia, Spain, occurring from 1997 to 2005. *International Classification of Diseases, Ninth Revision, Clinical Modification* codes were used to identify UGIB admissions associated with NSAIDs. To estimate the probability of association between UGIB and the use of NSAIDs, the Naranjo adverse drug reaction probability was used. Patients were categorized as high-risk to develop UGIB if they met ≥1 of the following risk criteria (*relevant risk factors*): aged ≥65 years (*age risk factor*); peptic ulcer disease or NSAID gastropathy occurring in the year before their hospital admission (*history risk factor*); and concomitant use of other NSAIDs, systemic corticoids, oral anticoagulants, or platelet aggregation inhibitors (*concomitant medication risk factor*). Patients were categorized as candidates to use gastroprotections if they met ≥1 of the relevant risk factors. Patients were categorized as users of gastroprotective

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treatment if they used proton pump inhibitors, histamine H_2-receptor antagonists, or misoprostol at hospital admission.

Results: This study comprised 209 cases of NSAID-induced UGIB (129 men, 80 women; mean [SD] age, 71.5 [13.8] years; 128 [61.2%] receiving acetyl salicylic acid [ASA], with 72 [34.4%] receiving low-dose [80–325 mg] ASA). Prevalence of relevant risk factors for UGIB were as follows: age, 158 (75.6%) patients; history, 37 (17.7%); and concomitant medication, 35 (16.7%). One hundred seventy-eight (85.2%) patients met ≥1 criterion for using a gastroprotective agent; 28 (15.6%) were actually using one. Only the history risk factor was significantly associated with the use of gastroprotective treatment (P = 0.007; odds ratio = 3.17).

Conclusions: In this study of NSAID-induced UGIB resulting in hospital admission, age was the most common risk factor. However, this criterion was not associated with the use of gastroprotective agents. A large number of cases were associated with the use of ASA, primarily in those receiving low doses. A significant lack of gastroprotective agent use was observed in patients who met the criteria to use them. (*Curr Ther Res Clin Exp*. 2007;68:107–119) Copyright © 2007 Excerpta Medica, Inc.

Key words: nonsteroidal anti-inflammatory drugs, upper gastrointestinal bleeding, hospital admissions, elderly, risk factors.

INTRODUCTION

NSAIDs have been found to be a significant cause of drug-related hospital admissions and deaths.[1,2] In Spain, NSAIDs are the most consumed drugs and are sixth in pharmaceutical expenditure.[3] They are considered the therapeutic class of drugs that is most frequently associated with self-medication, many times without an adequate analysis of risk-benefit. This especially has been found with the use of acetylsalicylic acid (ASA), which is a component of many over-the-counter (OTC) medicines.[4,5]

The therapeutic effects of NSAIDs have been associated with the risk for developing adverse events (AEs), mainly in the gastrointestinal (GI) tract,[6] such as NSAID gastropathy. This ranges from dyspeptic symptoms or signs to serious complications (eg, peptic ulcer or upper GI bleeding [UGIB]).[7] In a meta-analysis[8] of 24 randomized controlled trials, it was suggested that about 1 out of 100 patients who used ASA for a mean of 28 months developed UGIB. Peptic ulcers and UGIB might require hospitalization and have been associated with morbidity and mortality.[9] Approximately 15% to 30% of users of traditional NSAIDs develop mucosal injury associated with UGIB.[2] The relative increase in risk for GIB among NSAIDs users is estimated to be 4-fold.[2] An increased prevalence of NSAID toxicity also has been observed in elderly patients.[10] The prevalence of UGIB in elderly patients varies from 2.5% to 4.5%.[11]

The most relevant risk factors of developing NSAID-induced UGIB are[2,4,6,7,11,12]: (1) age ≥65 years[12–14] (age >60 years for some scientific associa-

tions[4,15]); (2) prior occurrence or history of peptic ulcer disease, including previous GI hemorrhage associated with NSAIDs[12,13,16]; and (3) concomitant use of other medications—systemic corticoids,[13] oral anticoagulants,[17] clopidogrel or ticlopidine,[18] alendronate,[19] or other NSAIDs, including low-dose ASA (80–325 mg/d)[20] (for ASA, the effect is dose-dependent[8,21]).

A search of MEDLINE and PUBMED was conducted for literature in the English or Spanish language published between January 1996 and December 2006 using the key terms *nonsteroidal anti-inflammatory drug*, *gastrointestinal bleeding*, and *prevention* [or *prophylaxis*]. From this search we identified recommendations or indications for the use of gastroprotective medications. The Spanish Association of Gastroenterology and the Spanish Society of Rheumatology recommend gastroprotective treatment use in patients aged >60 years who use, or will use, cyclooxygenase-2 (COX-2) nonselective-inhibitor NSAIDs, independent of the presence or absence of other risk factors.[15] Similarly, current UK clinical guidance[12] on NSAID use recommends gastroprotective treatment use in patients at high risk for NSAID-induced GI AEs (aged ≥65 years, history of gastroduodenal ulcer, GI bleeding, or gastroduodenal perforation, and/or use of concomitant medications that are known to increase the likelihood of upper-GI AEs). However, this evidence of the efficacy of gastroprotective treatment reducing UGIB is associated only with the use of coxibs.[22,23] Although the evidence of efficacy is limited, the lack of large-outcome studies to the contrary suggests that it does not take effect. Some systematic reviews[24,25] suggest that using a proton pump inhibitor and administering a double dose of histamine H_2-receptor antagonists or misoprostol are effective for preventing chronic NSAID-related endoscopic gastric and duodenal ulcers.

Additional risk factors for NSAID-induced UGIB include renal or liver dysfunction, cigarette smoking, high doses of NSAIDs, and chronic use of NSAIDs.[2,6–8,12,19]

As a consequence of the severity and frequency of UGIB, it is necessary to establish mechanisms to identify patients who are at high risk for developing NSAID-induced UGIB, and then employ preventive interventions which have been demonstrated as useful, such as gastroprotective treatment.[12,15,25,26] Since 1997, the Requena Hospital Pharmacy Service (Valencia, Spain) has maintained a database of drug-related UGIB resulting in hospital admissions. The aims of this study were to identify the most common risk factors associated with NSAID-induced UGIB resulting in hospital admissions and to explore the relationship between the use of gastroprotective treatment and relevant risk factors to NSAID-induced UGIB.

METHODS

Study Design

This study was a cross-sectional, retrospective, case-series analysis of NSAID-induced UGIB resulting in hospital admission to the Requena General Hospital, Valencia, Spain, occurring from 1997 to 2005. The health area of the hospital includes ~53,000 inhabitants. It is a rural zone, very dispersed, and dis-

tant from other hospitals. Cases of UGIB resulting in hospital admissions were determined following the same method as our previously published study[1] on drug-related UGIB resulting in hospital admissions. This study protocol was reviewed and approved by the Requena General Hospital Research Commission.

Detection System, Analysis and Verification of Cases of UGIB

A trained group of 1 physician (B.B.) and 2 pharmacists (J.L.M. and A.C.) followed a standardized approach to data collection. To detect UGIB hospital admissions associated with the use of NSAIDs, 1 physician (B.B.) reviewed the hospital admissions registration book on a monthly basis, searching for diagnoses of UGIB and those associated with UGIB, such as hematemesis (vomiting of blood) or melena (blood in stool).

To garner more GI bleeding admissions associated with NSAIDs and to discard nonbleeding and chronic diagnosis, 2 pharmacists (J.L.M. and A.C.) also reviewed the database of the clinical documentation department of the hospital on a monthly basis, searching for and identifying completed consultations with primary and secondary diagnosis codes according to *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* (*ICD-9-CM*).[27]

The main or primary *ICD-9-CM* diagnosis codes identified were as follows: 530.21, ulcer of esophagus (fungal, peptic) with bleeding; ulcer of esophagus due to ingestion of aspirin, chemicals, or medicines; 530.82, esophageal hemorrhage; 578.0, hematemesis; 578.1, melena; 578.9, hemorrhage of gastrointestinal tract, unspecified (gastric hemorrhage, intestinal hemorrhage); 531.0, acute gastric ulcer with hemorrhage; 531.00, acute gastric ulcer with hemorrhage, without mention of obstruction; 531.01, acute gastric ulcer with hemorrhage, with obstruction; 531.2, acute gastric ulcer with hemorrhage, with obstruction; 531.20, acute gastric ulcer with hemorrhage and perforation, without mention of obstruction; 531.21, acute gastric ulcer with hemorrhage and perforation, with obstruction; 533.0, acute peptic ulcer of unspecified site with hemorrhage (533.00 and 533.01, without or with mention of obstruction, respectively); 533.1, acute peptic ulcer of unspecified site with perforation (533.10 and 533.11, without or with mention of obstruction, respectively); 533.2, acute peptic ulcer of unspecified site with hemorrhage and perforation (533.20 and 533.21, without or with mention of obstruction, respectively); 534.0, gastrojejunal ulcer with hemorrhage (534.00 and 534.01, without or with mention of obstruction, respectively); 534.1, acute gastrojejunal ulcer with perforation (534.10 and 534.11, without or with mention of obstruction, respectively); 534.2, acute gastrojejunal ulcer with hemorrhage and perforation (534.20 and 534.21, without or with mention of obstruction, respectively); and 535.01, acute gastritis with hemorrhage.

Secondary diagnosis codes were as follows: E935.3, analgesics, antipyretics, and antirheumatics causing adverse effects in therapeutic use; E935.4, aromatic analgesics causing adverse effects in therapeutic use (acetanilid, paracetamol [acetaminophen], and phenacetin [acetophenetidin]); E935.5, pyrazole derivatives causing adverse effects in therapeutic use (aminophenazone [aminopyrine],

phenylbutazone); E935.6, antirheumatics (antiphlogistics) causing adverse effects in therapeutic use (gold salts, indomethacin); E935.7, other non-narcotic analgesics causing adverse effects in therapeutic use (aminopyrine-barbital complex); E935.8, other specified analgesics and antipyretics causing adverse effects in therapeutic use (pentazocine); and E935.9, unspecified analgesic and antipyretic causing adverse effects in therapeutic use.

One physician (B.B.) and 1 pharmacist (A.C.) checked all patient medical records to gather the necessary data regarding treatment and diagnoses. To estimate the probability of association between UGIB and the use of NSAIDs, the Naranjo adverse drug reaction probability[28] was used: a score of 1 to 4, possible; a score of 5 to 8, probable; and a score of ≥9, definite. A score of ≥5 was considered criteria for positive association between UGIB and NSAID use.

Study Population

All cases of drug-related UGIB resulting in hospital admission deemed to be associated with the use of NSAIDs were selected. Patients with UGIB associated with other drugs or without relevant information for the analysis were excluded.

Instruments

Information from UGIB cases associated with NSAIDs was collected using a data collection sheet. The patient data collected were as follows: age, sex, number of hospitalization days, current or historical diseases, concomitant use of other medication (NSAIDs, systemic corticoids, oral anticoagulants, platelet aggregation inhibitors), use of gastroprotective treatment (proton pump inhibitor, histamine H_2-receptor antagonists, or misoprostol),[23–25] and alcohol and tobacco consumption.

Patients were categorized as high-risk to develop an UGIB if they met ≥1 of the following risk criteria (*relevant risk factors*): aged ≥65 years (*age risk factor*)[12–14]; peptic ulcer disease or NSAID gastropathy occurring in the year before their hospital admission (*history risk factor*)[12,13,16]; and concomitant use of other NSAIDs, systemic corticoids, oral anticoagulants, or platelet aggregation inhibitors (*concomitant medication risk factor*).[12,13,17–20] Patients were categorized as candidates to use gastroprotections if they met ≥1 of the relevant risk factors. Patients were categorized as users of gastroprotective treatment if they used proton pump inhibitors, histamine H_2-receptor antagonists, or misoprostol at hospital admission.[23–25] Patients with a history of heart failure, cerebrovascular disease, coronary disease, chronic obstructive lung disease, cirrhosis, or renal failure were categorized as patients with associated comorbidities.[12]

The information collected regarding NSAIDs used was as follows: brand and generic name, dosage schedules, number of days of treatment, and drug dispensing category (OTC or prescription drugs). The NSAIDs were also grouped as traditional NSAIDs (all NSAIDs, excluding ASA), ASA used as a platelet antiaggregate (doses between 80–325 mg/d), and ASA used as an analgesic or antiinflammatory (doses >375 mg/d).

Statistical Analyses

Using patient and NSAID data, a database was created with Microsoft Office Access® 2003 (Microsoft Corporation, Seattle, Washington). Statistical analyses were performed using SPSS for Windows version 13.0 (SPSS Inc., Chicago, Illinois). Data were reported as mean (SD) or as percentage. The χ^2 test was used to compare proportions, and the Student *t* test was used to compare means, including odds ratio (OR) and 95% CI. Comparisons were analyzed using a 2-tail test and $P < 0.05$ was considered statistically significant. The Fisher exact test was used to compare categories that had <5 data sets. With a 95% CI, an OR of 3.0, and the number of patients included, this cross-sectional analysis had a power of 95% to detect significant differences between the use of gastroprotective agents in those patients with relevant risk factors and those without relevant risk factors.[2,12,13,25]

RESULTS

Two hundred twenty-six cases of drug-associated UGIB were found in the hospital database. Of these, 209 (92.5%) were attributed to NSAIDs, 4 (1.9%) were attributed to acetaminophen, 4 (1.9%) to metamizol, 3 (1.4%) to ticlopidine, and 3 (1.4%) to clopidogrel. In 3 (1.4%) cases the NSAID was not identified, as the only information appearing in the patients' clinical records was NSAID with no specific brand or generic name given. Of the 209 cases attributed to NSAIDs, 81 (38.8%) were associated with traditional NSAIDs, 72 (34.4%) to ASA with doses between 80 and 325 mg/d, and 56 (26.8%) to ASA with doses >325 mg/d. No selective COX-2–inhibiting drugs were associated with UGIB in this population.

This cross-sectional analysis comprised 209 cases (129 men, 80 women; mean [SD] age, 71.5 [13.8] years, median [range], 73 [25–98] years; mean [SD] hospitalization days, 4.6 [2.8], median [range], 4 [1–22] hospitalization days) of UGIB associated with NSAIDs, which occurred from 1997 to 2005. **Table I** shows the demographic and clinical characteristics with regard to sex.

Patients' Relevant Risk Factors for UGIB

Patients had a mean (SD) number of relevant risk factors of 1.1 (0.6); range, 0 to 3; median, 1.0; and mode, 1.0. The frequency of those risk factors were: age, 110 (52.6%); history, 11 (5.3%); concomitant medication, 8 (3.8%); age and history, 22 (10.5%); age and concomitant medication, 23 (11.0%); history and concomitant medication, 1 (0.5%); and age, history, and concomitant medication, 3 (1.4%). According to sex, there were no differences in the distribution or mean number of relevant risk factors, associated comorbidities, or cases associated with the use of OTC NSAIDs (**Table I**).

Indication and Use of Gastroprotective Medications

One hundred seventy-eight (85.2%) patients met ≥1 criterion for using a gastroprotective agent; 28 (15.7%) patients were actually using one. Among those

Table I. Demographic and clinical characteristics of patients admitted to the hospital for NSAID-induced upper gastrointestinal bleeding (UGIB).

Variable	Male (n = 129)	Female (n = 80)	All Patients (N = 209)
Age, mean (SD), y	72.3 (12.8)	70.2 (15.3)	71.5 (13.8)
Age, no. (%), y			
≥75	59 (45.7)	36 (45.0)	95 (45.5)
65–74	41 (31.8)	22 (27.5)	63 (30.1)
60–64	10 (7.8)	8 (10.0)	18 (8.6)
45–59	13 (10.1)	8 (10.0)	21 (10.0)
25–44	6 (4.7)	6 (7.5)	12 (5.7)
UGIB relevant risk factors,*†‡ mean (SD)	1.1 (0.6)	1.1 (0.7)	1.1 (0.6)
Distribution of the UGIB-relevant risk factors, no. (%)			
Age*	100 (77.5)	58 (72.5)	158 (75.6)
History†	24 (18.6)	13 (16.3)	37 (17.7)
Concomitant medication‡	19 (14.7)	16 (20.0)	35 (16.7)
None	18 (14.0)	13 (16.3)	31 (14.8)
Associated comorbidities,§ no. (%)	24 (18.6)	7 (8.8)	31 (14.8)
OTC drug use, no. (%)	32 (24.8)	18 (22.5)	50 (23.9)
Indication to the use of gastroprotective agents, no. (%)	111 (86.0)	67 (83.8)	178 (85.2)
Actual use of gastroprotective agents, no. (%)	15 (11.6)	13 (16.3)	28 (13.4)

OTC = over-the-counter.
*Aged ≥65 years.
†Presence or history of acid peptic disease, including previous gastrointestinal hemorrhage associated with NSAIDs.
‡Concomitant use of systemic corticoids, oral anticoagulants, clopidogrel, or other NSAIDs.
§Heart failure, cerebrovascular disease, coronary disease, chronic obstructive lung disease, cirrhosis, or renal failure.

28 patients, all had an indication to use it. The gastroprotective agents used were: proton pump inhibitors, 18 (64.3%); histamine H_2-receptor antagonists, 9 (32.1%); and misoprostol, 1 (3.6%). In the 31 patients without an indication to use gastroprotection, there were no patients using one. With regard to sex, there were no differences between the indication and use of gastroprotective treatment (**Tables I** and **II**).

Risk Factors and Use of Gastroprotective Agents

Age Risk Factor

Among the 158 (75.6%) patients aged ≥65 years, 23 (14.6%) were using gastroprotective medications. Also, 5 (9.8%) of the 51 patients aged <65 years were using gastroprotective medications. Therefore, there were no significant differ-

Table II. Use of gastroprotective agents and hospitalization stay with regard to upper gastrointestinal bleeding (UGIB) risk factors in patients admitted to hospital for NSAID-induced UGIB (N = 209).

Risk Factor	No. of Patients	Use of Gastroprotective Agents, No. (%)	*P*	Hospitalization Stay, Mean (SD), d	*P*	UGIB Relevant Risk Factors, Mean (SD)*	*P*
Age,* y							
≥65	158	23 (14.5)	0.418	4.9 (3.0)	0.005	1.3 (0.5)	<0.001
<65	51	5 (9.8)		3.6 (1.9)		0.4 (0.5)	
Sex							
Male	129	16 (12.4)	0.592	4.7 (2.7)	0.550	1.1 (0.6)	0.754
Female	80	12 (15.0)		4.4 (3.1)		1.1 (0.7)	
History†							
Yes	37	10 (27.0)	0.007	3.6 (2.3)	0.017	1.8 (0.6)	<0.001
No	172	18 (10.5)		4.8 (2.9)		1.0 (0.6)	
Concomitant medication‡							
Yes	35	7 (20.0)	0.208	4.3 (2.1)	0.510	1.9 (0.6)	<0.001
No	174	21 (12.1)		4.6 (3.0)		1.0 (0.5)	
Associated comorbidities§							
Yes	31	4 (12.9)	0.930	4.5 (2.4)	0.795	1.2 (0.6)	0.258
No	178	24 (13.5)		4.6 (2.9)		1.1 (0.7)	
OTC NSAIDs							
Yes	50	2 (4.0)	0.025	3.9 (2.4)	0.061	0.9 (0.6)	0.019
No	159	26 (16.4)		4.8 (2.9)		1.2 (0.7)	

OTC = over-the-counter.
*Age risk factor was associated with patients aged ≥65 years.
†Presence or history of acid peptic disease, including previous gastrointestinal hemorrhage associated with NSAIDs.
‡Concomitant use of systemic corticoids, oral anticoagulants, clopidogrel, or other NSAIDs.
§Heart failure, cerebrovascular disease, coronary disease, chronic obstructive lung disease, cirrhosis, or renal failure.

ences between those with the age risk factor and those without (**Table II**). In patients aged ≥75 years, the percentage of gastroprotective agent use (14.7%) was similar to the percentage of patients aged ≥65 years who were using them (14.5%). The mean (SD) age was similar in the 28 patients who used gastroprotection compared with those 181 patients who did not (72.0 [13.4] vs 71.4 [13.9]).

History Risk Factor

Among the 37 (17.7%) patients with the history risk factor, 27.0% (10/37) were using a gastroprotective agent. This percentage was significantly larger than that of the 10.5% (18/172) of patients without the history risk factor who were using a gastroprotective agent (P = 0.007; OR = 3.17; 95% CI, 1.21–8.24) (**Table II**).

Concomitant Medication Risk Factor

Among the 35 (16.7%) patients with a concomitant medication risk factor, 20.0% (7/35) were using a gastroprotective agent. This percentage was larger than that of patients without this risk factor who were using a gastroprotective agent (12.1% [21/174]) (**Table II**), but the difference was not statistically significant.

Associated Comorbidities

Of the 31 (14.8%) patients with associated comorbidities, 12.9% (4/31) were using a gastroprotective agent. This was similar to the percentage of patients without this risk factor who were using a gastroprotective agent (13.5% [24/178]) (**Table II**).

OTC NSAIDs

Of the 50 (23.9%) cases of UGIB that were associated with OTC NSAIDs, 40 (80.0%) patients had an indication to use gastroprotective agents. Of those patients, 5.0% (2/40) were using gastroprotective medications. Of the 159 cases of UGIB associated with prescription NSAIDs, 139 (87.4%) patients had an indication to use gastroprotective agents, of those, 26 (18.7%) were using gastroprotective medications. Consequently, there were no significant differences between the use of OTC and prescription NSAIDs with regard to the indication to use gastroprotective agents (80.0% vs 87.4%). However, in the patients with an indication to use gastroprotective agents, a significantly larger percentage of the prescription NSAID patients were actually using a gastroprotective agent (18.7%) when compared with the percentage of OTC NSAID patients (5.0%) (P = 0.036; OR = 0.23; 95% CI, 0.02–0.99).

Similarly, of the 50 patients with UGIB associated with OTC NSAIDs, only 4.0% (2/50) were using a gastroprotective agent. This percentage was significantly lower than the 16.4% (26/159) of patients with UGIB associated with prescription NSAIDs who were using gastroprotective medications (P = 0.025; OR = 0.21; 95% CI, 0.02–0.91) (**Table II**).

DISCUSSION

This study selected patients who were hospitalized for UGIB and retrospectively describes patient characteristics and risk factor profiles of 209 cases of NSAID-induced UGIB that resulted in hospital admissions to Requena General Hospital, Valencia, Spain. This study explored associations between the use of gastroprotective treatment and relevant risk factors to NSAID-induced UGIB; therefore, the results do not imply causations. Among the cases examined, most (128 [61.2%]) were associated with the use of ASA, mainly (72 [56.3%]) with low doses (80–325 mg/d). This result suggests the need to dispense this drug, including OTC products, with the same caution as any other NSAID.[5,29] Additionally, 50 cases of NSAID-induced UGIB were associated with OTC NSAIDs (40 cases with an indication of gastric protection and 2 cases actually using gastroprotection treatment). These findings suggest the need to implement programs of pharmaceutical care focused on the use of oral nonprescription analgesics at a community pharmacy level.[4]

Although a majority (61.7% [129/209]) of the UGIB cases was in male patients, the frequency of the relevant risk factors of NSAID-induced UGIB did not vary according to patient sex.

In this group of NSAID-induced UGIB cases, we found a significant lack of use of gastroprotective agents in patients who met the criteria to use them (84.8% [151/178]). However, this study selected patients who were hospitalized for UGIB and this finding might be expected. In our study, patients' mean (SD) age, 71.5 (13.8) years, was similar to that reported by Lim and Heatley[30] (70.5 [15.2] years) in a group of 43 patients who used NSAIDs and developed GI hemorrhage identified by endoscopy. Although age was the most frequent risk factor in our study, this criterion was not associated with the use of gastroprotective agents. In a study by Laine et al,[13] the relative risk for developing NSAID-induced GI hemorrhage in persons between 65 and 74 years old was found to be 2.4, and 3.9 in persons aged >74 years. In fact, among the 3 risk factors and criteria that indicated its use, only the history risk factor was significantly associated with the use of gastroprotective medications. This differs from recommendations[12,15] and published works[13,17,20,25] that suggest that the use of gastroprotective cotherapy should be considered in patients at high risk for developing NSAID-induced UGIB. It also suggests the need to carry out informative and educational activities to improve the use of this preventive intervention in this group of patients.

In this study, 14.5% of patients aged ≥65 years used gastroprotection, a percentage that was mirrored in patients aged ≥75 years (14.7%). This frequency is apparently lower than the 36% of patients aged ≥75 years reported by Hartnell et al.[31] The difference might be associated with the type of population studied; the study by Hartnell et al examined patients aged ≥65 years receiving treatment with antiarthritic drugs. In turn, in our study, the total percentage of patients who were using gastroprotective medication (13.4%) was similar to the 11% reported by Lim and Heatley.[30] These results suggest the under-use of this preventive intervention. Due to the lack of strong evidence,[22,23] it is necessary to

develop clinical trials that will assess the effectiveness of this strategy. Studies comparing the assessment of practice (eg, use of gastroprotective agent with selective COX-2–inhibiting drugs), patient preference, long-term tolerance, and the cost-effectiveness of gastroprotective therapies are also needed.[32]

In 84.2% (176/209) of the cases of NSAID-induced UGIB, the age of the patients was >60 years. This is in agreement with recommendations[15] made by the Spanish Association of Gastroenterology and the Spanish Rheumatology Society for using preventive interventions in patients aged >60 years. These recommendations should be assessed in a prospective, longitudinal, controlled study to compare the tolerability of NSAIDs plus gastroprotective treatment versus NSAIDs alone in this age group.

Study Limitations

Because our study had several limitations, the results must be interpreted with caution. This study included only patients who were hospitalized for UGIB, so there is an important selection bias inherent in this population. This study was a cross-sectional analysis of retrospective case series, therefore, it lacked a control group; causal associations could not be established. In the majority of the cases observed (89.5% [187/209]), the estimating probability of NSAID-induced UGIB was probable (5–8 points using the Naranjo adverse drug reaction probability scale). Some statistical analyses and comparisons were conducted in a very small number of cases, so the analysis was likely underpowered to detect differences. Finally, the absence of fixed information on clinical factors, such as precise NSAID schedules, adherence to NSAID treatment, *Helicobacter pylori* assessment, and smoking and alcohol consumption, might have resulted in an underestimation of the risk for UGIB. Therefore, it is probable that some patients were on gastroprotective medications just before admission but were not recorded as such on the data collection sheet.

CONCLUSIONS

In this retrospective analysis of database case series of NSAID-induced UGIB resulting in hospital admission, age was the most common risk factor. However, this criterion was not associated with the use of gastroprotective agents. A significant lack of gastroprotective agent use was observed in patients who met the criteria to use them (84.8% [151/178]). A large number of cases (61.2% [128/209]) were associated with the use of ASA, primarily in those receiving low doses (80–325 mg/d).

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