Upper Gastrointestinal Toxicity of Nonsteroidal Anti-Inflammatory Drugs in African-American and Hispanic Elderly Patients

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Objectives: To determine the upper gastrointestinal (UGI) toxicity of nonsteroidal anti-inflammatory drugs (NSAIDs), in African-American and Hispanic elderly patients.

Setting: Inner-city community hospital.

Methods: Retrospective review of records of 698 patients, 65 to 101 years old. Upper gastrointestinal (UGI) symptoms and history of NSAIDs consumption were recorded over a 12-year period. Twenty White and 25 Asian patients were excluded. Another 101 patients were excluded because of incomplete data or because endoscopy was not performed. Patients were stratified as NSAID-users or non-users, and the data were analyzed.

Results: Among the 552 patients, the most common lesion was gastro-duodenal erosions (34%), while common symptoms were abdominal pain (71%) and bleeding (54%). Both lesions and symptoms were higher among NSAID-users than non-users ($P<.05$). Endoscopic therapy was given to 296 patients, and was successful in stopping the bleeding and/or delaying surgery in 70% of the patients. Helicobacter pylori tests were done in 238 patients, and were positive in 47% of the patients. Overall 144 deaths occurred (26%). Mortality was significantly higher among elderly patients who used NSAIDs compared to those who did not use them ($P<.05$).

Conclusions: Our study suggests a higher association between NSAID use and UGI toxicity than is reported in current literature. Patients suffering from UGI toxicity of NSAIDs may remain asymptomatic until complications occur, therefore a high index of suspicion and a low threshold for endoscopy are essential, especially in elderly patients. Avoiding NSAIDs whenever possible, substituting less toxic COX-2 inhibitors, monitoring risk, and providing cotherapy with proton pump inhibitors (PPI), or misoprostol, as suggested in the literature, may decrease NSAIDs associated morbidity and mortality in this patient population. (*Ethn Dis*. 2003;13:528–533)

Key Words: Gastrointestinal, Nonsteroidal, Anti-inflammatory, African-American, Hispanic, Elderly

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed medications and are used worldwide for the treatment of rheumatic disorders.[1] The beneficial effects of NSAIDs in relieving pain and inflammation are well known; however, the therapeutic advantage of these drugs, in certain cases, may be clouded by their toxicity, which if severe enough can cause significant morbidity and even mortality. Erosive esophagitis and esophageal strictures occur more frequently in patients with diseases requiring NSAIDs.[2] Moreover, aspirin, the most popular agent used universally for cardiovascular and cerebrovascular prophylaxis, also has the potential to cause significant GI toxicity in the form of gastric erosions, ulcers, and GI bleeding. NSAIDs are estimated to be responsible for more than 17,000 deaths annually in the United States. NSAID use in the elderly is associated with more frequent hospitalization and other serious consequences of NSAID toxicity.[3] In particular, elderly patients using NSAIDs are at higher risk of peptic ulcer disease, GI bleeding and death.[4,5] Although the precise mechanism of NSAID-induced GI damage remains unknown, important factors include direct epithelial toxicity, disruption of protective gastric mucosal barrier and interference with cytoprotective action of prostaglandins by inhibiting their synthesis,[6] and impairment of mucosal microcirculation.[7]

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Although data in the literature pertaining to NSAID toxicity is widely available, this problem is not well studied in African-American and Hispanic patients. Our study focused on this population since these 2 ethnic groups constitute the majority of our patients.

Methods

Study Population and Study Site

The King-Drew Medical Center is an inner-city community teaching hospital serving a predominantly African-American and Hispanic population. Records of 698 patients, 65 to 101 years of age, over a twelve-year period, with UGI symptoms (abdominal pain, indigestion, gastrointestinal bleeding, heartburn and dysphagia), were reviewed retrospectively and history of NSAID consumption was recorded. The source of these records included inpatient and outpatient charts of patients, and gastroenterology consultation reports. Twenty White and 25 Asian patients were excluded. Because endoscopy was not performed, and/or data were incomplete, a further 101 patients were also excluded, leaving 552 African-American and Hispanic patients with complete endoscopic records for subsequent review.

Statistical Analysis

Data were analyzed using either the 2-tailed chi-square test (Yates correction) or the Fisher exact test (in sparse data) to assess the statistically significant differences between the NSAID-users and the non-users. Odds ratios were calculated for the gastrointestinal toxicity related outcome variables (lesions and symptoms) to estimate the odds of hav-

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ing the outcome in the NSAID-users relative to the non-users. To assess the effect of the demographic variables on the association between NSAID use and the UGI toxicity, data were analyzed by age group, gender and race/ethnicity. Crude and adjusted odds ratios were estimated and a chi-square test was performed. The statistical analyses were performed using SPSS (Statistical Package for Social Science version 10, 2000; SPSS Inc, Chicago, Ill) and Epi Info (windows version 2.2, 2002; Center for Disease Control and Prevention [CDC], Atlanta, Ga).

RESULTS

The study comprised 304 African-American patients (140 males, 164 females) and 248 Hispanic patients (114 males, 134 females) (Table 1). The prevalence of smoking was 37% among NSAID non-users and 39% among NSAID-users. The prevalence of alcohol use was 32% among NSAID non-users and 30% among NSAID-users. Both smoking and alcohol use were not significantly different between NSAID-users and non-users ($P>.05$).

Endoscopic findings in the 552 study patients shown in Table 2, demonstrated that the most common findings were gastro-duodenal erosions (34%), gastric ulcers (26%), and duodenal ulcers (22%). Patients were stratified as NSAID-users (54.5%) and non-users (45.5%). Gastro-duodenal erosions, gastric ulcer and esophageal erosions or ulcers were significantly more likely to occur in NSAID-users than in non-users ($P<.05$).

Table 1. Patient demography

Variables	African Americans (*N*=304)		Hispanics (*N*=248)	
Age in years	Males (*N*=140) *N* (%)	Females (*N*=164) *N* (%)	Males (*N*=114) *N* (%)	Females (*N*=134) *N* (%)
65–75	76 (54.3)	88 (53.7)	61 (53.5)	74 (55.2)
76–85	52 (37.1)	58 (35.4)	43 (37.7)	45 (33.6)
86–101	12 (8.6)	18 (10.9)	10 (8.8)	15 (11.2)

Symptoms

Presenting symptoms and their correlation with NSAIDs consumption were also studied. The most widely observed symptoms were found to be abdominal pain, UGI bleeding, indigestion, heartburn, and dysphagia in decreasing order (Table 3). All of the symptoms, except abdominal pain, were significantly more likely to occur in NSAID-users than non-users ($P<.05$); although, abdominal pain was more common in NSAID non-users ($P=.00001$). In 296 patients (174 NSAID-users and 122 non-users), upper gastrointestinal (UGI) bleeding was the presenting symptom. Individuals taking NSAIDs were 3 times more likely to present with UGI bleeding than than were non-users ($P<.05$). Upper gastrointestinal (UGI) bleeding and its association with the NSAID use varied significantly by age of the patients although odds increased among older patients ($P<.05$) (Table 4).

Aspirin use alone or in combination with other NSAIDs and its association with UGI bleeding was also studied (Table 5). Independent of the type of NSAIDs used, users were 3 times more likely to present with UGI bleeding than non-users. Patients who were taking aspirin were at the highest risk of presenting with UGI bleeding compared to patients who did not consume any form of NSAIDs ($P=.0003$) (Table 5).

Endoscopic therapy (heater probe coagulation of bleeding vessel, injection of saline, epinephrine, variceal sclerosis

Table 2. Endoscopic finding of upper gastrointestinal lesions in 552 elderly patients

Lesion	NSAID			Odds Ratio	*P* value
	Total (*N*=552) **N* (%)	Non-users (*N*=301) *N* (%)	Users (*N*=251) *N* (%)		
Gastro-duodenal erosions	189 (34)	58 (19)	131 (52)	4.5	.0001
Gastric ulcer	145 (26)	63 (21)	82 (33)	1.8	.001
Duodenal ulcer	122 (22)	59 (20)	63 (25)	1.4	.12
Esophageal erosions or ulcers	72 (13)	24 (8)	48 (18)	2.7	.0004
Esophageal varices	55 (10)	28 (9)	27 (11)	1.2	.57
Angiodysplasia	44 (8)	24 (8)	20 (8)	1.0	.99
Mallory Weiss tear	33 (6)	17 (6)	16 (6)	1.1	.72
Portal hypertensive gastropathy	30 (5)	16 (5)	14 (5)	1.1	.89
Dieulofoy's lesion	29 (5)	15 (5)	14 (5)	1.1	.76
Esophageal strictures (non-malignant)	28 (5)	10 (3)	18 (7)	2.3	.06
Esophageal cancer	22 (4)	13 (4)	9 (3)	0.8	.83
Gastric cancer	20 (4)	12 (4)	8 (3)	0.8	.79

* Total exceeds 552 and 100% because 82 patients (15%) had more than one lesion.

Table 3. Presenting symptom in relation to NSAID use

Symptom	NSAID Total (*N*=552) *N (%)	NSAID Non-users (*N*=301) *N* (%)	NSAID Users (*N*=251) *N* (%)	Odds Ratio	*P* value
Abdominal pain	392 (71)	247 (82)	145 (58)	0.3	.00001
Indigestion	289 (52)	139 (46)	150 (60)	1.7	.001
Bleeding	296 (54)	122 (41)	174 (69)	3.3	.00001
Heartburn	166 (30)	78 (26)	88 (35)	1.5	.019
Dysphagia	88 (16)	39 (13)	49 (19)	1.7	.04

* Total exceeds 552 and 100% because 320 patients (58%) had more than one symptom.

or banding) was given to 296 patients with upper GI bleeding (174 NSAID-users and 122 non-users) and was successful in stopping the bleeding and/or delaying surgery in 209 (97 NSAID-users, 112 non-users) or (70.6%) of the treated patients. Out of the 89 non-responders to endoscopic therapy (56 NSAID-users, 33 non-users), 69 patients underwent emergency surgery. Twenty non-surgical patients (12 NSAID-users, 8 non-users) and 15 post-operative patients (9 NSAID-users, 6 non-users) died during the index hospital admission. Dilation of esophageal strictures was attempted in 27 patients with benign strictures; these patients showed significant improvement in their symptoms. When the same procedure was attempted in 12 patients with esophageal carcinoma, 6 patients showed only temporary improvement in dysphagia. Helicobacter pylori tests, (biopsy and/or serology), were done in 238 patients (112 NSAID-users, 126 non-users), and were positive in 112 (47%) of the tested patients (50 NSAID-users, 62 non-users).

Mortality

Overall, 144 deaths occurred (26%), 88 (35%) in NSAID-users and 56 (18.6%) in non-users ($P<.05$). The overall mortality varied significantly by age groups of the patients (group 1=12.7%, group 2=38.9%, group 3=55.7%, $P=.0001$). Mortality also varied slightly by gender (male=29.9%, female=22.8%, $P>.05$). Mortality did not vary by race/ethnicity of the patients (African American=25%, Hispanic=27.4%, $P>.05$). Factors associated with increased mortality included NSAID use, presence of co-morbid conditions, older age group, and probably male gender. The association between NSAID use and mortality was analyzed controlling for age of the patient. Adjusting for age of the patient, NSAID-users were 3 times more likely to die than non-users (Table 6).

No death was directly associated with endoscopic intervention; however, there were a few transient side effects including hypotension in 7 patients, cardiac arrhythmias in 5 patients, and respiratory depression in 4 patients. All of these side effects resolved after a period of observation and symptomatic supportive therapy when necessary.

Table 4. Comparison of Upper Gastrointestinal Bleeding (UGIB) between patients taking aspirin, non-aspirin NSAIDs, and patients who had not taken any NSAIDs—adjusting for age group of the patient

Crude Odds Ratio=3.26 Age Adjusted Odds Ratio=3.35 (2.37–4.91) *P*=.0000001

Age group (years)	Number of Aspirin and/or NSAID Users UGIB Yes	Number of Aspirin and/or NSAID Users UGIB No	Number of No aspirin and No NSAIDs* UGIB Yes	Number of No aspirin and No NSAIDs* UGIB No	Odds Ratio	*P* value
65–75	90	59	62	88	2.17	.001
76–85	61	18	45	71	5.35	.0003
86–101	20	0	15	20	26.7	.0002

* Reference group.

DISCUSSION

Nonsteroidal anti-inflammatory drugs (NSAIDs) toxicity is the most common drug induced disease. Spectrum of NSAID toxicity varies from dyspeptic symptoms to frank GI bleeding, perforation, and death.[8]

Endoscopic findings vary from mere mucosal congestion to erosions and ulceration.[9] Risk of GI complication among NSAID-users increases up to 10-fold as compared to NSAID-non-users in the general population. Reported cases of NSAID toxicity represent merely the tip of the iceberg. About 100 million NSAID prescriptions are dispensed annually in the United States, but many more cases remain unnoticed, as many patients use non-prescription NSAIDs available over the counter, without consulting a physician. Although the association between NSAID use and GI complications is well established, and there are multiple studies in the literature about upper gastrointestinal toxicity of NSAIDs,[10–12] the literature describing this information (or topic) in African-American and Hispanic patients is sparse. Our study demonstrated an association between NSAID use and GI toxicity among the minority population. The odds of various UGI complications among the NSAID-users were up to 4.5 times higher than the non-users. In a case-control study comparing hospitalized patients to hospital and visitor control, investigators observed an association between NSAIDs and UGI toxicity

Table 5. Comparison of Upper Gastrointestinal Bleeding (UGIB) between patients taking aspirin, non-aspirin NSAIDs, both, and patients who had not taken any NSAIDs

	UGIB			
	Yes	No	Odds Ratio	*P* value
Number of NSAID-users	174	77	3.3	.0001
Aspirin only	51	20	3.7	.0003
Non-aspirin NSAIDs (NANSAIDs)	53	27	2.9	.0006
Aspirin and NANSAIDs	70	30	3.4	.0006
No aspirin and no NANSAIDs*	122	179	1	reference

* Comparison group.

especially duodenal ulcer (odds ratio, 1.1), gastric ulcer (odds ratio, 5) and bleeding (odds ratio, 3.5).[13] Our study showed comparable results for duodenal ulcer and bleeding and lower odds for gastric ulcer. The possible reason could be due to study design and selection of subjects. In an earlier study, the incidence of UGI hemorrhage in African-American and Hispanic elderly patients was much higher than in studies not focused on this population.[14] A high prevalence of UGI bleeding where more than half of the minority patients presented with UGI bleeding was shown in our study.

The retrospective design of our study represented a significant weakness, restricting collection of data from the available records only and not affording us the opportunity to interview the patients and follow their clinical course in a prospective manner. However, the lesions found were similar to those described in the literature where the most common lesions found on endoscopy included gastro-duodenal erosions and/or ulcers. A significant difference existed in NSAID-users and NSAID non-users with increased numbers of such lesions in the former. Although NSAID-users developed lesions similar to NSAID non-users, there was an increase in frequency and a tendency of lesions to remain asymptomatic until a complication occurred. For example, GI bleeding was the first manifestation of NSAID toxicity in 72 of 180 (40%) NSAID-users as compared to 31 of 118 (26%) NSAID non-users. This observation concurs with the literature that clinical symptoms, events and endoscopic findings may vary significantly, reinforcing the view that silent peptic ulceration tends to occur in the elderly patients.[15] Of note is the complication of GI bleeding in the elderly patients, who may present without overt hematemesis, hematochezia, or melena. One or more of these extraintestinal manifestations may be the only clue before endoscopic diagnosis of the culprit lesion.[16] Traditionally NSAIDs are known to cause gastric ulcers rather than duodenal ulcers although delayed healing and increased risk of bleeding may occur in a preexisting duodenal ulcer.[17] However, in our study there was a slight increase in duodenal ulcers as well in NSAID-users as compared to NSAID non-users. This finding may be due to smaller number of patients, other risk factors or yet unidentified factors.

The role of Helicobacter pylori (HP) in NSAID induced gastrointestinal lesions is controversial and therapeutic guidelines are still evolving. Initially it was thought that there was no close association between NSAID-ulcers and Helicobacter pylori; however, the current literature suggests that eradication of Helicobacter pylori before starting NSAID therapy may diminish subsequent ulcer development.[18] In spite of this, tests for Helicobacter pylori were done only in 238 (43%) of our patients, of whom 112 (47%) were positive. Previous studies have reported an overall prevalence of HP around 32%–35%; this increased with age to 41%–57% in the age group 70–85 years.[19,20] Utilizing the available records, it was not possible to determine whether Helicobacter pylori was eradicated or how it influenced the clinical outcome in these 112 patients.

Several meta-analyses of NSAID-risk assessment trials have been done previously. The results of these studies showed that peptic ulcer bleeding was more common (2.7 to 3.3 times) in NSAID-users than non-users and results did not differ between aspirin and non aspirin NSAIDs.[21] In our study the prevalence of UGI bleeding from all the lesions was also higher (3.3 times) in NSAID-users than non-users and more so among aspirin users than non aspirin NSAIDs. We were not able to ascertain fully in our study whether this might be due to study design or differences in patient morbidity and severity of the concomitant disease(s).

Mortality was significantly higher

Table 6. Odds ratio of mortality for NSAID-users vs NSAID non-users adjusting for age of the patients

Crude Odds Ratio=2.36 Adjusted Odds Ratio=3.20 (CI=2.12–5.32) *P*=.0005

Age (Years)	NSAIDs Users		NSAIDs Non-Users*		Odds Ratio	*P* value
	Dead	Alive	Dead	Alive		
65–75	22	127	16	134	1.45	.3
76–85	49	33	28	88	4.67	.0009
86–101	17	3	12	23	10.86	.0008

* Comparison group.

among NSAID-users than non-users, a finding that is consistent with the literature where NSAID-users had higher death rates than non-users.[8] The possible explanation may be due to differences in the associated comorbidity, multiple lesions, poor general conditions and severity of the disease among the NSAID-users.

Head-to-head comparison between our study and others described in literature may not be possible because of variation of study design, methodology and possibly differences in population characteristics.

Nonsteroidal anti-inflammatory drugs (NSAIDs), smoking and alcohol consumption are all described as risk factors for gastrointestinal perforation.[22] Although a significant number of our patients had a history of smoking and alcohol use, we did not find many patients with gastrointestinal perforation. This finding may be due to the relatively small number of patients in our study. However, vigilance should be observed while treating patients who have these risk factors, and prophylactic therapy with a proton pump inhibitor may be considered if NSAID use is mandatory.

Since racial/ethnic minorities suffer disproportionately high morbidity and mortality from several chronic diseases, they probably have a higher risk for complications associated with GI lesions and bleeding. This high risk is consistent with the mortality found in our study (26%). The high morbidity and mortality in our study could be due to limited availability of health education and preventive services as well as barriers to timely medical care to this minority population.

Although our study found no significant difference in mortality between racial/ethnic groups and gender, there was an abrupt increase in mortality with age. The reason for this difference is unclear but it is consistent with those mentioned in the literature[21] such as, the presence of co-morbidity and delay in diagnosis.

Avoiding NSAIDs whenever possible, using them in lowest effective dose and for shortest possible duration . . . may decrease NSAID-associated morbidity and mortality.

CONCLUSIONS

Our study of 552 patients undergoing endoscopy for GI symptoms, suggests a higher association than the current literature indicates between NSAID use and UGI toxicity. In this sample of elderly African-American and Hispanic patients, mortality was significantly higher in elderly subjects, but there were no significant gender or racial differences. Nonsteroidal anti-inflammatory drugs (NSAIDs) associated UGI toxicity may remain asymptomatic until complications occur; therefore, a high index of suspicion and a low threshold for endoscopy are essential especially in elderly patients. Avoiding NSAIDs whenever possible, using them in lowest effective dose and for shortest possible duration, substituting to less toxic COX-2 inhibitors[23] risk monitoring, co-therapy with proton pump inhibitors (PPI) or misoprostol in high risk patients, as per literature[24–25] may decrease NSAID-associated morbidity and mortality. Prospective studies examining clinical and healthcare system related risk factors for NSAID toxicity in minority patients, and outcomes with specific therapeutic strategies are warranted.

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AUTHOR CONTRIBUTIONS

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