Original Article

Frequency of NSAID Induced Peptic Ulcer Disease

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Abstract

Objective: To determine the frequency of peptic ulcer disease in patients on nonsteroidal anti-inflammatory drugs (NSAID).

Methods: Record of eight hundred and twenty consecutive patients undergoing upper gastrointestinal (GI) endoscopy; from January 1998 to December 2000 were reviewed. The endoscopic diagnosis varied from gastritis, peptic ulcer to duodenitis. The use of NSAID was documented by reviewing medical records of patients with peptic ulcer.

Results: Peptic ulcers were found in 43% (353/820) patients. NSAID associated peptic ulcers were identified in 14.7% (52/353) patients. Diclofenac and aspirin were most common NSAIDs associated with peptic ulcers in 32.7% (17/52) and 30.7% (16/52) patients, respectively. Duodenal ulcer was more common than gastric ulcer 65.3% (34/52) and 42.3% (22/52), respectively. H. pylori infection was present in 46% (24/52) of the cases. NSAIDs treatment and / or H. pylori infection compared to non NSAIDs and non H. pylori infected peptic ulcer disease were significantly associated with gastric ulcer ($p = 0.004$) and duodenal ulcer ($p = 0.009$) respectively.

Conclusion: NSAID-associated peptic ulcer disease is common in Pakistan and most frequently associated with gastric and duodenal ulcer. H. pylori infection is common in association with NSAID related peptic ulcers (JPMA 56:218;2006).

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain and inflammation worldwide.[1] They are available over the counter with widespread use for various indications. The use of NSAID is associated with well-recognized risks of gastrointestinal toxicity.[2] The drugs commonly associated with gastroduodenal ulceration include NSAIDs, steroids, antibiotics and chemotherapy agents. Most peptic ulcers not due to Helicobacter pylori (H. pylori) are caused by NSAIDs.[3] Peptic ulcer disease symptoms vary from dyspeptic symptoms to haematemesis and malaena. It may prove fatal in some patients. The various mechanisms of NSAID induced gastric injury include: a) damage of the gastric epithelium by intracellular accumulation of these drugs in an ionized state, b) reducing the hydrophobicity of the mucous gel layer by changing the action of surface-active phospholipids, c) suppression of the prostaglandin synthesis, d) injury due to neutrophils adherence to the endothelium of gastric microcirculation.[4-7] Established risk factors for NSAIDs associated peptic ulcer disease include advanced age, female gender, past history of peptic ulcer, non-selective NSAIDs, concomitant use of anticoagulants or corticosteroids, H. pylori infection and heavy consumption of alcohol.[8] The risk of gastrointestinal bleeding increases steeply with age, and the excess risk from nonaspirin NSAIDs is much higher in the elderly than in young subjects, even when the relative risk is assumed to remain constant with age.[9] The excess risk in women is attributed to their age >65 years, higher dose of NSAIDs per kilogram body weight and much steeper dose response curve in women than in men.[10] H. pylori and NSAIDs damage the stomach by different mechanisms. However, neutrophil-induced mucosal injury might be a common pathogenetic pathway shared by these two factors. This is consistent with the finding that H. pylori-induced neutrophil infiltration is associated with an increased risk of ulcers in chronic NSAIDs users.[11] As the rate of H. pylori infection is falling, the proportion of NSAIDs related-peptic ulcer has risen.[12] Although no NSAID is totally safe, it has been demonstrated that NSAIDs may be ranked according to relative GI toxicity.[10] Depending on the plasma levels and the half-life of the NSAIDs, the risk is short-lived with ibuprofen than piroxicam with a long plasma half-life.[13,14] This is attributed to the differential inhibition by the NSAIDs of the 2

isoenzymes involved in the synthesis of prostaglandins, cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2). Improved GI safety is observed with drugs that spare COX-1, the isoenzyme responsible for gastroprotection. In contrast, the more toxic drugs demonstrate greater COX-1 inhibition.[15,16] Alcohol consumption of > 5 drinks at a time increased the risk significantly above that seen in moderate drinkers and non-drinkers.[10] The aim of this study was to determine the frequency of NSAIDs related-peptic ulcer disease in dyspeptic patients undergoing upper gastrointestinal endoscopy in a tertiary care hospital.

Patients and Methods

This retrospective study was conducted at Aga Khan University Hospital, Karachi, Pakistan. Medical records of 820 consecutive patients undergoing upper gastrointestinal (GI) endoscopy from January 1998-December 2000 were reviewed who attended gastroenterology department and had endoscopic diagnosis of gastritis, peptic ulcers or duodenitis. The history of NSAIDs use was collected by reviewing the patient's medical record with age, sex, previous diagnosis, current indication, dosage and duration of NSAID use. The risk factors associated with peptic ulcer disease such as smoking, alcoholism, pan eating and tobacco chewing with concomitant use of medications such as anticoagulants and corticosteroid were also noted. The endoscopic lesions were classified into gastritis, peptic ulcer, and duodenitis. Peptic ulcer was defined as a break of about 3mm in the mucosal surface and then categorized according to site i.e., fundus, corpus, antral, pylorus and duodenal ulcer as proximal (D1) or distal (D2). Rapid urease test (CLO test) and histopathology results were noted.

Results were expressed as mean standard deviation, median with range for all continuous variables (age, dose etc) and number (percentage) for categorical data (e.g. gender, etc.). However, univariate analysis was performed by using Pearson's Chi-square, Fisher-exact test and the difference in mean was evaluated by independent sample T test where ever appropriate. A p-value less than 0.05 was considered statistically significant. Statistical interpretation of data was performed using the computerized software program SPSS version 10.0.

Results

The frequency of various NSAIDs used by the patients and associated with peptic ulcer is shown in Table 1.

The most common indication for prescribing NSAID was arthritis in 40% (21/52) and muscular aches in 36.5% (19/52) patients (Table 1).

Duration of NSAID use varied from less than 1 month for 52% (27/52) to greater than 1 month for 48% (25/52) patients. Risk factors for NSAID related peptic ulcer were noted in only 31% (16/52) patients. Smoking and concomitant steroid therapy were the commonest risk factors (Table 1). There were no

Table 1 NSAID-related peptic ulcer disease clinical details, risk factors and associated diseases.

	NSAID	Non-NSAID
Total No.	52	301
Sex:		
Male	30	204
Female	22	97
Age:		
Range(years)	16-80	16-90
Male		
Mean	59 ± 13.48	48 ± 16.78
Female		
Mean	54 ± 15.83	48 ± 15.42
Risk factors:		
1. Smoking	9 (17.3%)	44 (14.6%)
2. Corticosteriods therapy	5 (9.6%)	17 (5.6%)
3. Alcoholism	1 (1.9%)	13 (4.3%)
4. Pan eating	1 (1.9%)	9 (3%)
Disease		
1. No co-morbids	45 (86.5%)	239 (79.4%)
2. Chronic liver disease	5 (9.6%)	40 (13.3%)
3. Cancer	1 (1.9%)	1 (1.9%)
4. Bleeding disorder	1 (1.9%)	-
5. Tuberculosis	-	7 (2.3%)
NSAID used		
Diclofenac	17 (33%)	
Aspirin (enteric coated)	16 (31%)	
Piroxicam	5 (10%)	
Ponstan	4 (8%)	
Indmethacin	3 (5%)	
Ibuprofen	3 (5%)	
Flubiprofen	2 (4%)	
Naproxen	2 (4%)	
Indication for NSAID use		
1. Arthritis	21 (40 %)	
2. Muscular aches	18 (35 %)	
3. Orthopedics problems	9 (17%)	
4. Fever	4 (8%)	

Table 2.

Site of Peptic ulcer	NSAID			Non-NSAID		
	H.P Infection (n=24)	Non H.P Infection (n=28)	P-value	H.P Infection (n=175)	Non H.P Infection (n=126)	P-value
Gastric ulcer	6 (25%)	11 (39%)	0.379	34 (20%)	48 (38%)	0.002
Gastric ulcer + Duodenal ulcer	2 (8%)	3 (11%)		12 (7%)	9 (7%)	
Duodenal ulcer	16 (67%)	13 (46%)		123 (25%)	68 (54%)	
None		1 (4%)		6 (3%)	1 (1%)	
Gastric Ulcer			0.566			0.612
Fundus	1 (13%)	1 (29%)		3 (7%)	6 (11%)	
Body	4 (50%)	4 (29%)		15 (33%)	18 (32%)	
Antrum	-	6 (43%)		23 (50%)	23 (50%)	
Pylorus	3 (37%)	3 (21%)		5 (10%)	10 (17%)	
Duodenal ulcer						
D1	16 (89%)	16 (100%)	0.487	122 (90%)	67 (87%)	0.724
D2	-	-		6 (4%)	4 (5%)	
D1 + D2	2 (11%)	-		7 (5%)	6 (8%)	

HP: Helicobaoter Pylori

Table 3. Univariate analysis of NSAID and or H. pylori infection associated peptic ulcer disease with Non-NSAID and H. pylori negative peptic ulcer disease.

Non-NSAID and non H. pylori infection		NSAID and H. pylori infection	P value
-		+	
Glastric ulcer			
-	69 (30%)	159 (70%)	0.004
+	57 (46%)	68 (54%)	
Duodenal ulcer			
-	49 (46%)	58 (54%)	0.009
+	77 (31%)	169 (69%)	

NSAIDs associated peptic ulcers (Table 1). Of 820 patients, 43% (353/820) had peptic ulcer disease, 15% (52/353) had NSAID-related and 85% (301/353) patients had non-NSAID use peptic ulcer. In NSAID-related peptic ulcer disease 57.6% (30/52) were males and 42.4% (22/52) were females (Table 1). Their age ranged from16-80 years. The mean age of male patients with NSAID-related peptic ulcer was 59 ± 13.48 years and in females 54 ± 15.83 years. NSAID related gastric ulcer and duodenal ulcer when compared with non-NSAID related gastric ulcer and duodenal ulcer (p= 0.260) and (p= 0.464) respectively. H. pylori were positive on rapid urease test or histopathology in 46% (24/52) of NSAID- related peptic ulcers and negative in 54% (28/52). In non-NSAID related peptic ulcers, H. pylori were positive in 58% (175/301) and negative in 42% (126/301). NSAID-related peptic ulcer disease with or without H. pylori infection when compared with non-NSAID related peptic ulcer disease and without H. pylori infection (p=0.004) for gastric ulcer and (p=0.009) for duodenal ulcer (Table 3).

Discussion

NSAIDs and H. pylori infection are two most important independent factors in peptic ulcer disease. Their relative frequency as the cause of peptic ulcer varies and is partly related to the use of NSAIDs and frequncy of H. pylori infection in a population. The use of NSAIDs and H. pylori infection is both common in elderly population.[17] There has been an increase in admissions due to peptic ulcer haemorrhage and perforation among elderly people attributed to NSAIDs and low-dose aspirin use.[12] In USA, prescribed NSAIDs account for about 25% of all reported adverse drug reactions. An estimated 16500 patients with arthritis die every year from the gastrointestinal related side effects of NSAIDs.[2] It is now recognized that NSAIDs induced gastrointestinal

toxicity, is primarily due to inhibition of gastric mucosal prostaglandin synthesis, which subsequently impairs the cytoprotective factors. Development of highly selective cyclo-oxygenase (COX)-2 inhibitors has followed better understanding of the mechanisms involved in NSAIDs mediated damage of the stomach.[18]

In this study, low dose aspirin therapy and diclofenac were equally common as NSAIDs associated with peptic ulcers. This is consistent with previous studies and reflects that no dose is safe from gastrointestinal toxicity.[12] However, among NSAIDs, diclofenac has been considered to be at the safer end of the spectrum for gastrointestinal (GI) risk on account of its short half-life.[10] NSAIDs were found to be commonly prescribed for arthritis and almost equally for nonspecific symptoms. The various risk factors and conditions that have an additive effect on the gastrointestinal toxicity of NSAIDs were not prominent in our patients. However, patients with NSAIDs related-peptic ulcer disease did have a higher mean age, which is an established risk factor (Table 1). Peptic ulcers associated with NSAIDs were seen in the the first part of duodenum followed by gastric body. This might be attributed to high incidence of H. pylori infection in these patients. In a local prospective study regarding risk factors associated with peptic ulcer disease, 80% had duodenal ulcer (DU) and 20% gastric ulcer (GU) with a DU: GU ratio of 4:1.[19] Intake of NSAIDs was the second major risk factor in 40% of PUD patients, particularly associated with GU (50%).[19] In another study those taking a relatively higher dose of aspirin (300mg) or soluble aspirin complained of more symptoms. However, endoscopy did not show a corresponding rise in mucosal injury in them.[20] NSAID related-peptic ulcers were associated with H. pylori infection in 46 % of our cases. Also, H. pylori infection was more commonly associated with NSAIDs related duodenal ulcer than gastric ulcer in this study. This may be consistent with an increased incidence of H. pylori infection in our part of the world. However, a larger population based study is required to confirm these findings, as the sample size was small.

The clinical implications of this study are that as none of these non-selective NSAIDs are devoid of gastrointestinal toxicity, it would be safer to restrict their use in nonspecific symptoms. In elderly, options available are between choosing an NSAID with known low incidence of GI toxicity in a lowest effective dose. If a non-selective NSAID cannot be stopped, concomitant use of a proton pump inhibitor (PPI) or misoprostol will reduce the incidence of gastric and duodenal ulcer.[21] NSAID related peptic ulcer disease was found to be common with or without concomitant H. pylori infection in our study. There was a statistically significant association of NSAID-related peptic ulcer disease with or without H. pylori infection as compared to non-NSAID and non-H. pylori peptic ulcer disease. It is still unclear whether H. pylori infection plays a synergistic role with NSAIDs in causing peptic ulcer. A recent meta-analysis showed H. pylori infection increased the risk of ulcers in NSAID users to 3.5 times that of non-infected NSAID users.[22] There are studies both in favour of and against eradicating H. pylori infection that reduces the risk of ulcer in chronic NSAID s users.[23-25] In conclusion, there is a relatively high incidence of NSAID associated peptic ulcers and they are equally common with or without concomitant H. pylori infection.

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