

Upper Gastrointestinal Bleed Induced By Non-Steroidal Anti-Inflammatory Drugs/Aspirin In Jamaica

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Citation

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Abstract

Background: Gastrointestinal disturbances are the most common adverse effects of NSAIDs and ASA. Upper gastrointestinal bleeding (UGIB) occurs in over 2-4% of NSAIDs/ASA users. **Objectives:** To review patients admitted with upper gastrointestinal bleed induced by NSAIDs/ASA at the University hospital of the West Indies between January 2001 to December 2007. **Methods:** Patients admitted between January 2001 to December 2007 with upper gastrointestinal bleed caused by NSAIDs/ASA were reviewed. Data regarding age, gender, hospital stay and drugs used were obtained. Descriptive frequency statistics was used to analyse the data collected. **Results:** Of 88 patients reviewed, 46 (24 females and 22 males) were admitted with UGI bleed induced by NSAIDs/ASA and 42 patients (13 females and 29 males) had non-NSAIDs/ASA induced UGIB. The mean age in the NSAIDs/ASA induced UGI haemorrhage group was significantly older compared to the non-NSAIDs/ASA group (62 vs 51 years). The patients hospitalized for NSAIDs/ASA induced UGIB had significantly shorter hospital stays being 3.48 times more likely (95% CI= 1.27-9.56; Z= 2.42, p <0.05) to be hospitalized for 1-3 days than non-NSAIDs/ASA patients. Aspirin and diclofenac were most frequently implicated followed by ibuprofen and indomethacin, mefenamic acid, piroxicam and rofecoxib. **Conclusions:** NSAID/ASA induced UGI bleeding occurred in older patients. Hospital stay in the NSAID/ASA group was shorter. Aspirin and diclofenac are responsible for majority of the drug induced haemorrhages that occurred.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are a chemically heterogeneous group of organic acids that share certain therapeutic actions such as anti-inflammatory, analgesic or anti-pyretic and adverse effects. Aspirin or acetylsalicylic acid (ASA) on the other hand is utilised for its analgesic and cardiovascular protective properties. NSAIDs and ASA elicit their action by inhibiting cyclo-oxygenase (COX) enzyme involved in the biosynthesis of prostaglandin and thromboxane A₂ but in a distinctive molecular way. NSAIDs inhibits COX enzymes (COX1, COX 2) reversibly while aspirin irreversibly inhibit COX activity, covalently modifying COX-1 and COX-2 ultimately disrupting a variety of prostaglandin and thromboxane formation (1).

The NSAIDs share many common adverse reactions. Gastrointestinal complications including gastric erosions, ulcers, and perforation are the most dominant adverse reactions associated with NSAIDs/ASA resulting in significant morbidity and mortality (1,2,3). Peptic ulcers are encountered in 15-30% of NSAIDs users and significant upper gastrointestinal events occur clinically in 3-4% of

NSAIDs users annually (3,4). ASA and NSAIDs are major causes of upper gastrointestinal bleeding (UGIB) worldwide with an an increasing mortality rate among users with UGI bleeding (5,6). More than 30 million individuals are estimated to take NSAIDs daily by prescriptions and over-the-counter purchases (4). Because of the widespread use of NSAIDs/ASA, their serious upper gastrointestinal tract complications constitute a major public health concern. To reduce the morbidity associated with NSAIDs/ASA, it will be necessary to establish estimates for individual drugs and groups of patients with different risk profiles (7).

In Jamaica there has been no previous study conducted to investigate NSAIDs/ASA induced UGI bleeding. This study investigated patients admitted with UGIB induced by NSAID and ASA at the University Hospital of the West Indies between January 2001 to December 2007.

PATIENTS AND METHODS

All patients admitted to the University Hospital of the West Indies, Jamaica, between January 2001 to December 2007 with upper gastrointestinal bleeding were eligible for

inclusion. The charts of patients with the International Classification of Disease (ICD) codes from the World Health Organisation were retrieved with codes relating to upper gastrointestinal bleeding and haemorrhages due to non-steroidal anti-inflammatory drugs and aspirin. Codes for the following complications were retrieved; Gastrointestinal bleed, NSAIDs, ASA, Gastric Ulcer, Duodenal Ulcer, Peptic Ulcer. Data collected included; admission date, discharge date, age, gender, diagnosis, symptoms, NSAIDs/ASA use, indication, co-morbidity and number of days in hospital.

The data was evaluated using descriptive frequency statistics and relative risk (RR) analysis using SPSS version 16.

RESULTS

There were 263 cases admitted with upper GI bleeding identified from the ICD-10 codes between January 2001 to December 2007 and 100 cases were randomly selected from this group for study. Of the 100 cases selected 88 case records were located and confirmed to have upper gastrointestinal bleed. Of the 88 patients studied, 46 had upper GI bleed induced by NSAIDs/ASA. There were, 37 female patients, of which 24 had UGI bleed induced by NSAIDs/ASA while 13 had UGI bleeding which was non NSAIDs/ASA induced. There were 22 males with UGI bleed that was induced by NSAIDs/ASA while 29 male patients had UGI bleeding that was non-NSAID induced. Females hospitalized for upper GI haemorrhage, were significantly more represented among NSAIDs/ASA induced cases (RR = 1.69 (95% CI= 0.99-2.86), Z= 1.93, P=0.05). There was no increased risk among males users of the drugs, neither was there any difference in gender distribution among NSAIDs/ASA induced UGI bleeding.

Patients admitted with NSAID/ASA induced UGI bleed (mean, 62 years) were significantly older than the non-NSAIDs/ASA patients (mean, 51 years).

Table 2 shows the NSAIDS/ASA implicated in upper gastrointestinal haemorrhage. Aspirin (17) and diclofenac (17) were most frequently involved, followed by ibuprofen (2) and indomethacin (2). In patients admitted with UGI haemorrhage 50% of females and 14% males were being treated for arthritis.

The patients hospitalized for NSAIDs/ASA induced upper GI bleed had much shorter hospital stays being 3.48 times more likely (95% CI= 1.27-9.56; Z= 2.42, p <0.05) to be hospitalized for 1-3 days than non-NSAIDs/ASA patients (Table 1). In contrast, the non-NSAID/ASA group was more

likely to be hospitalized for more than 3 days.

Figure 1

Table1: Patient data and hospital stay

	NSAIDs/ASA associated	Non-NSAIDs/ASA
Mean age (range)/yrs	62 (10- 97)	51 (18-85)
Male	22	29
Female	24	13
Hospitalized 1-3 days	16	4
Hospitalized >3 days	13	36

Figure 2

Table 2: Drugs associated with UGI haemorrhage.

Drug Name	Number of patients (n=46)	% of total
ASA	17	37
Diclofenac	17	37
Indomethacin	2	4
Ibuprofen	2	4
Piroxicam plus Rofecoxib	1	2
Mefenamic acid	1	2
NSAIDs/ASA unknown	6	13

DISCUSSION

There is a strong association between NSAID use and upper gastrointestinal emergency hospital admissions, which is higher in females (2). In this study, similar findings were obtained as there was a greater number of females admitted with UGI bleed that was induced by NSAIDs/ASA in comparison to those who had UGIB which was non-NSAIDs/ASA induced. This difference in the aetiology of UGI bleed in females may be due to more frequent administration of medications for pain. In a study conducted in Jamaica, it was concluded that females were more likely to use painkillers than males (8). Also, in the present study,

significantly more females were on treatment for arthritis than males. In general, men have twice the risk for serious GI bleeding than women (9).

The mean age at which UGI bleed was induced by NSAIDs/ASA in this study was significantly greater (62 vs. 51 years) than in patients with non-NSAIDs/ASA UGI bleed. In general, UGIB increases with age and previous studies indicate that NSAIDs/ASA induced UGI bleed occurs at an older age (2,4). In fact, increasing age is an independent risk factor for gastrointestinal complications in NSAID users. In a systematic review of case-control and cohort studies on serious gastrointestinal tract complications and NSAIDs, published between 1990 and 1999, nonsteroidal anti-inflammatory drug users with advanced age or a history of peptic ulcer had the highest absolute risks. The increased risk was maintained during treatment and returned to baseline once treatment was stopped (7).

The other main predisposing factors for UGI bleed such as prior history of UGIB, *Helicobacter pylori* infection or peptic ulcer disease was not investigated in this study. Both NSAID/ASA and *H. pylori* independently confer increased risk for UGI bleeding, with a synergistic interaction between these two factors, which leads to increased incremental risk (4,10). *H. pylori* infection was present in 69.9 % in an urban community of Jamaica and in 55 % of patients undergoing upper endoscopy (11,12). The eradication of *H. pylori* infection significantly decrease the risk of recurrent bleeding in patients taking aspirin (5).

The overall risk for hospitalization resulting from gastrointestinal complications was estimated at approximately 1% per year in persons taking NSAIDs in the USA and patients taking NSAIDs are 6.45 times more likely to be hospitalized for a gastrointestinal complication than are nonusers (4). In the present study, the duration of hospital stay was significantly shorter in the NSAID/ASA group which may indicate milder bleeds compared to other causes.

Aspirin and diclofenac was most commonly implicated in UGI bleeding in this series. A previous study indicated that azapropazone and piroxicam had the highest risk for UGI bleeding whilst the others NSAIDs had relative similar risks (13). Aspirin is widely used for the primary and secondary prevention of acute coronary events and it is estimated that millions worldwide take aspirin daily for the prevention of heart attack and stroke (14). However, the use of aspirin increases the risk for major bleeding events, primarily gastrointestinal bleeding events, in both men and women

(15). Aspirin doubles the risk of upper gastrointestinal bleeding even at doses as low as 75 mg daily (16). Up to 15 percent of those taking aspirin who have a history of bleeding from ulcers had recurrent bleeding within one year (17). Before commencing aspirin it is recommended that clinicians discuss the possible side effects and benefits with patients who require primary or secondary prevention for coronary heart disease and stroke.

Concomitant therapy of gastro-protective agents such as proton-pump inhibitors, H₂ antagonist and prostaglandin analog along with NSAIDs/ASA can reduce the occurrence of UGI haemorrhage. Concurrent therapy with a proton-pump inhibitor is a standard treatment for patients receiving aspirin who are at risk for peptic ulcer. (17). Testing and treating for *H. pylori*, especially in patients requiring long term aspirin should be considered as an alternative option, especially in Jamaica with a high prevalence of *H. pylori* infection. Where possible selective COX-2 inhibitors may be substituted for the traditional NSAIDs. This may result in less UGI haemorrhages, as studies have shown that in patients with rheumatoid arthritis, treatment with a COX 2 inhibitor was associated with significantly fewer clinically important upper gastrointestinal events than treatment with naproxen, a nonselective inhibitor (18,19). In the present study, the majority of the females were using NSAIDs for management of arthritis, thus suggesting a need to consider the use of COX-2 selective drugs to females.

There are several limitations in the present study. Being a retrospective study limits the amount of information available to be retrieved. Thus drug information relating to dosage, duration and frequency was limited. The study group size was small, thus preventing generalisation.

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