Risk of Upper and Lower Gastrointestinal Bleeding in Patients Taking Nonsteroidal Anti-inflammatory Drugs, Antiplatelet Agents, or Anticoagulants

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BACKGROUND & AIMS: **Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or low-dose aspirin is associated with increased risk of upper gastrointestinal bleeding. There is little evidence on the risk of lower gastrointestinal bleeding with NSAIDs, antiplatelet agents (APAs), or anticoagulants. We aimed to quantify the relative risk (RR) of upper and lower gastrointestinal bleeding associated with use of NSAIDs, APAs, or anticoagulants.**

METHODS: **We performed a case-control study that used data collected from consecutive patients hospitalized for gastrointestinal bleeding (563 upper, mean age, 63.6 ± 16.7 years and 415 lower, mean age, 70.8 ± 13.8 years), confirmed by endoscopy or other diagnostic procedures. Unhospitalized patients were used as controls (n = 1008) and matched for age, hospital, and month of admission. Drug use was considered current when taken within 7 days or less before hospitalization. RRs and 95% confidence intervals (CIs) were estimated by unconditional logistic regression analysis.**

RESULTS: **Use of anticoagulants, low-dose aspirin, and other drugs (non-aspirin-APA, 82.3% thienopiridines) was associated with upper and lower gastrointestinal bleeding; the risk was 2-fold higher for anticoagulants (RR, 4.2; 95% CI, 2.9–6.2) than for low-dose aspirin (RR, 2.1; 95% CI, 1.4–3.3) or other non-aspirin-APA drugs (RR, 2.0; 95% CI, 1.6–2.6). NSAID use was also associated with increased risk of gastrointestinal bleeding and greater for upper (RR, 2.6; 95% CI, 2.0–3.5) than lower gastrointestinal bleeding (RR, 1.4; 95% CI, 1.0–1.9). Use of proton pump inhibitors was associated with reduced risk of upper, but not lower, gastrointestinal bleeding.**

CONCLUSIONS: **Anticoagulants, low-dose aspirin, NSAIDs, and other non-aspirin-APA drugs are associated with increased risk of upper and lower gastrointestinal bleeding. Use of anticoagulants appears to be the strongest risk factor for gastrointestinal bleeding.**

Keywords: Stomach; Intestine; Peptic Ulcer; Small Bowel; Colon; Side Effect; Complication.

It is well-established that nonsteroidal anti-inflammatory drug (NSAID) treatment is associated with increased risk of peptic ulcer and non-variceal upper gastrointestinal bleeding (UGIB).[1,2] However, growing evidence suggests that NSAIDs can also damage the lower gastrointestinal (GI) tract.[3,4] Several studies have shown that NSAID use is associated with mucosal damage of the small bowel identified as mucosal breaks.[5,6] Reports also suggest that NSAIDs can also damage the colon.[7,8] New evidence is becoming available concerning small bowel or colonic damage associated with aspirin use, but the clinical relevance of these lesions is still uncertain.[9] Evidence on the risk of lower gastrointestinal bleeding (LGIB) associated

Abbreviations used in this paper: APA, antiplatelet agent; ASA, low-dose aspirin; CI, confidence interval; GI, gastrointestinal; H_2RA, H_2 receptor antagonist; LGIB, lower gastrointestinal bleeding; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; RR, relative risk; UGIB, upper gastrointestinal bleeding.

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with other non-aspirin antiplatelet or anticoagulant agents is related only to diverticular bleeding and is also very scarce,[10] whereas it is clear that use of these drugs is growing in a progressively elderly population.[11]

Different studies have shown that the use of proton pump inhibitors (PPIs) prevents upper GI damage and the risk of upper GI complications but is unable to prevent NSAID-associated small bowel mucosal damage.[1,6] No data are available concerning the impact of PPI use on lower GI complications. During the last decade, there were reports showing a decreasing trend in hospitalizations that are due to upper GI complications, whereas lower GI complications showed a small but sustained increasing trend.[12] Whether these changes are, at least in part, due to change in prescription habits (eg, higher PPI use) and a result of increased risk of LGIB associated with use of NSAIDs or low-dose aspirin (ASA), non-aspirin antiplatelet agents (APAs), or anticoagulant agents is not known.

This study was designed to provide evidence on the risk of both upper and lower GI bleeding associated with NSAIDs, ASA, non-aspirin APAs, anticoagulants, and PPIs. By providing this information we should be able to evaluate simultaneously and compare the risk of bleeding associated with the use of these drugs in both the upper and the lower GI tract and provide some evidence to further explain current trends in hospitalizations that are due to GI complications, which should help to design potential prevention strategies in these patients.

Methods

Study Design and Population

Case-control study with prospective case ascertainment and data collection was carried out between 2009 and mid-2013. Cases and controls were collected through a network of general hospitals integrated within the Spanish Association of Gastroenterology and the Biomedical Investigation Network Center of hepatic and digestive diseases (CIBERehd). Overall, eligible participants were 20–90 years old with non-variceal GI bleeding who had been free of liver disease, coagulation disorders, or malignancies for the previous 5 years.

Definitions

A case is a patient hospitalized because of GI bleeding (hematemesis, melena, hematochezia, or red blood per rectum), which was confirmed by hospital personnel. A bleeding event was considered to be UGIB event if hematemesis was observed by hospital staff and/or there was either blood in the stomach or a lesion with stigmata of bleeding was present at the time of the upper GI endoscopy. A bleeding event was considered to be LGIB event when a lesion with stigmata was found below the angle of Treitz by endoscopic or radiologic procedures, or when no lesions were identified in the upper GI tract at the endoscopic procedure performed within 24 hours of emergency hospital admission and no hematemesis was reported or evidenced. All other events not complying with these definitions and without a clearly identifed site were considered as unspecified GI bleeding events.

Cases with the following conditions were excluded: (1) bleeding caused by gastroesophageal or intestinal varices, GI cancer, Mallory–Weiss lesions, associated coagulopathy, and esophagitis; (2) patients with unreliable sources of information; (3) patients refusing to participate; and (4) in-hospital bleeding patients.

Controls matched by age (±5 years), gender, hospital, and month of admission were selected. Controls were obtained from people accompanying or visiting hospitalized patients. When the identification of a control under this condition was unsuccessful, unselected people referred to external general outpatient's laboratory office for blood extraction (as part of routine general analysis) were used.

For exposure, drug use was considered to be current when the drug was taken up to 7 days before the index date. It was considered to be past when drug use ended more than 1 week before the index date. Non-use was considered in individuals not reporting use. The index date for cases was the first day when the GI bleeding episode was objectively noticed, and for controls it was the day of interview. We analyzed the effects of individual NSAIDs among current single users. ASA was defined as any dose no greater than 300 mg/day. Non-aspirin APA drugs were clopidogrel, ticlopidine, dipyridamole, and trifusal. PPI use included all types of PPIs available on the market during the study period. All doses were considered to be PPI use. H_2 receptor antagonist (H_2RA) included any dose of ranitidine and famotidine, because cimetidine use was negligible.

For GI disorder history, a person was defined as having no history of upper GI disorder if he/she reported no history of dyspepsia or ulcer (uncomplicated or complicated) before the index date. A person was defined as having a history of dyspepsia only if he or she did not also report a history of peptic ulcer. Finally, a person was defined as having a history of peptic ulcer without or with complications (bleeding or perforation) when he or she reported so and found or provided previous hospital reports that confirmed the diagnosis. All of these groups were mutually exclusive. In the same way, we classified cases and controls as having or not having a history of lower GI diseases (complicated and uncomplicated). A person was defined as having a history of lower GI complications if he/she reported bleeding or perforation history caused by lesion (GI cancers were excluded, as defined in the exclusion