Review Article [Sharma & Sharma, 6(1): Jan., 2015:4209-4213]
CODEN (USA): IJPLCP ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES
(Int. J. of Pharm. Life Sci.)

Gastrointestinal Bleeding in Cardiac Patients

Jaya Sharma and Prashant Sharma
IIP, Indore (MP) - India

Abstract

Cardiac patients are a fast emerging population vulnerable to gastrointestinal bleeding (GIB) due to their use of antithrombotic medications. This review will quantify the GIB risk of cardiac patients prescribed antithrombotic medications, summarize risk-management strategies and highlight knowledge gaps. As the American population ages, it is anticipated that there will be an increased incidence of upper and lower GIB related to age-specific disease, higher burden of co morbidity and increased use of anticoagulants, ant platelets and aspirin to treat cardiac disease. New evidence has highlighted the significant and clinically relevant GIB risk. The increased use of aggressive ant platelet and anticoagulant therapies will alter our current understanding of the epidemiology of GIB.The magnitude of gastrointestinal risk in this vulnerable patient population is still relatively unexplored due to a paucity of literature. This review will highlight changing GIB trends and explore current knowledge regarding GIB risk in cardiac patients. An emphasis on a multidisciplinary approach to the care of these patients will be supported, which involves active patient participation and collaboration between cardiologists and gastroenterologists. Finally, risk-minimization strategies will be suggested and knowledge gaps will be identified.

Key-Words: Cardiac Patients, Bleeding, GIB

Introduction

The American population is growing older and it is estimated by 2030 there will be over 60 million adults 65 years and older in the United States. This phenomenon will be associated with an increase in age-related co morbidities, including ischemic heart disease, hepatic, renal and malignant disease and diverticulitis.[1–4] This review evaluates epidemiologic implications of a new emerging population at risk of gastrointestinal bleeding (GIB) – the aging cardiac population. Current risk-minimization strategies will be reviewed and knowledge gaps will be identified to focus attention on future research needs.

Gastrointestinal Bleeding Epidemiology: Old and New

In the 1980s and 1990s *Helicobacter pylori* and nonsteroidal anti-inflammatory drugs (NSAIDs) shaped our perspective of clinical GIB. GIB epidemiology was focused on peptic ulcer-related disease (PUD) and the impact of proton pump inhibitors (PPIs) and eradication of *H. pylori* in decreasing morbidity and mortality. Our attention then turned to the emergence of NSAID, aspirin (ASA) and anticoagulant-related lower GIB (LGIB), and the impact of age-related comorbidities, including ischemic heart disease and diverticulosis.[1,4,5]

*** Corresponding Author**
E.Mail: prashant_sharma659@yaoo.co.in

The influence of comorbidity as an important independent risk factor for poor GIB outcomes, when compared with independent pharmacologic risk factors, has been recently explored and highlighted in the literature.[4,6,7]

The most vulnerable population for upper (UGIB) and LGIB are elderly cardiac patients. These patients have multiple risk factors for GIB, including advanced age, a high burden of comorbidity and polypharmacy of anticoagulants, ASA and antiplatelet agents (i.e., antithrombotic agents). They often have preexistent mucosal defects that are at risk for bleeding, including diverticulosis, arteriovenous malformation and angiodysplastic lesions.[8] It is estimated by 2030, 40.5% of adult Americans will have at least one cardiovascular disease requiring at least one antithrombotic agent.[3] If projections for crude cardiovascular disease are superimposed on the United States population growth curve it is estimated that 27.2 million older Americans will have at least one cardiovascular condition treated by an antithrombotic medication for primary or secondary cardioprophylaxis by 2030.[3]

The burden of cardiac comorbidities among the elderly often results in prescription antithrombotic agents in dual and triple combinations [i.e., complex antithrombotic therapy (CAT)].[9] A Spanish cohort study of 1219 patients following percutaneous coronary intervention demonstrated 96.9% were

prescribed dual antiplatelet therapy [ASA + thienopyridine (e.g., clopidogrel)] at the time of discharge and only 76.6% were prescribed a PPI. Within 6 months, 2.2% had one or greater major GIB events, all of which were severe and required hospitalization. LGIB occurred more frequently than UGIB (P=0.012) and one case of LGIB was fatal.[8] This study lacked the power to fully elucidate determinants of GIB. However, nonbleeding patients tended to be younger (66 versus 70 years; P = 0.06) and a prior peptic ulcer history and warfarin therapy were both associated with a three to four-fold increased risk of GIB.[8]

The role of CAT in causing clinically significant GIB events has recently been described by Abraham *et al.* [10] in *Circulation*. These data demonstrate the magnitude of risk and the frequency of events. The 1-year number needed to harm associated with ASA and an anticoagulant agent to incur one additional UGIB, LGIB, bleed-related transfusion or hospitalization is 93 [95% confidence interval (CI): 34–544], 18 (95% CI: 10–37), 51 (95% CI: 24–182) and 67 (95% CI: 30–214), respectively. Dual antiplatelet therapy with ASA and an antiplatelet therapy is associated with a number needed to harm of 93 (95% CI: 34–544) for UGIB, 18 (95% CI: 10–37) for LGIB, 51 (95% CI: 24–182) for bleed-related transfusion and 67 (95% CI: 30–214) for bleed-related hospitalization. Triple therapy with ASA plus anticoagulant plus antiplatelet is associated with a risk of harm in as few as 23 patients (LGIB), 52 (UGIB), 25 (bleed-related transfusion) and 45 (bleed-related hospitalization).[10]

The clinical utilization of novel oral anticoagulants (NOAC; i.e., dabigatran, rivaroxaban, apixaban and edoxaban) has added a new dimension to the landscape of GIB. These agents differ from warfarin, a vitamin K antagonist, with regard to mechanism of action, metabolism, time to maximum effect, half-life, excretion and the ability to monitor the antithrombotic effect.[11] Meta-analysis of randomized controlled data (RCT) demonstrate the risk of GIB with novel oral anticoagulants is 45% greater than warfarin alone, when used in patients with acute coronary syndrome (ACS), atrial fibrillation, deep venous thrombosis, pulmonary embolus and following orthopedic surgery [odds ratio (OR) 1.45; 95% CI: 1.07–1.97].[12] The bleeding risk for patients prescribed triple CAT using NOAC is also now emerging. NOAC prescribed in combination with ASA or a thienopyridine agent (i.e., clopidogrel, prasugrel or ticagrelor) after ACS, is associated with a three-fold increase in major bleeds (OR 3.03; 95% CI: 2.20–4.16), which translates to a number needed to harm of only 111 patients.[13] In contrast, the same meta-analysis clarified the potential cardiac benefit as expressed by a number needed to treat of 77.[13] These data demonstrate a very narrow threshold for risk-benefit that many elderly cardiac patients will have to navigate when treating multiple cardiac comorbidities in the future.

Patient-centered Care: Including the Patient in Medication Decision-making

These new drugs and complex patients highlight the necessity for a new clinical paradigm to help balance the risk of GIB versus the clear cardiac benefit of antithrombotic agents prescribed in elderly patients. We can no longer think in terms of clinical silos with the cardiologist and the gastroenterologist working at cross-purposes, independently and without consideration of the patient's preferences for care. A multidisciplinary approach to risk-benefit management is critical and best achieved when a cardiologist and a gastroenterologist comanage high-risk cardiac patients together. Regardless of the nature of the multidisciplinary team, physicians cannot lose focus on the most important person on the team, the patient. He or she alone will reap potential clinical benefit and suffer the consequences of adverse drug events. Inclusion of the patient's perspective in medical decision-making is a key guiding principle of patient-centered care.

Research among cardiac patients demonstrates their desire to be engaged in the medication decision-making.[14] Data published recently in *Circulation* endorse shared decision-making to increase the likelihood that patients receive the care they need in a manner that is consistent with the best available clinical evidence, while still being respectful of the individual's values and preferences.[14] During shared decision-making, patients and their providers engage in a deliberate process of information exchange regarding preferences and goals of care. Patients engage in the process to the degree they are willing, making explicit their values and preferences to reach a consensual decision with clinicians regarding a shared treatment plan.

Among cardiac patients prescribed CAT, a patient's experience and perception of drug regimens will change over time as they gain experience with the potential risks and benefits. Data have shown that experiential knowledge of CAT is likely to influence future adherence behaviors to prescribed drug regimens and adverse drug event monitoring.[15] Given the likelihood that a patient's perceptions of risk-benefit associated with CAT will change over time, shared decision-making should not be considered a static event. Rather, it should be viewed as an iterative

process, involving patient-doctor negotiation, revisited periodically as the patient experiences new clinical events that will undoubtedly shape their priorities for cardioprophylaxis versus GIB prevention.[14–16]

Cardiogastroenterology: A Collaborative Clinical Approach

The rapid diffusion of new antiplatelet and anticoagulant drugs on the market has ushered in a new era for the risk-management of GIB among cardiac patients. The rapid uptake of these agents and prescription of the same in dual and triple combinations has occurred in some cases without adequate postmarketing data to fully inform risk of GIB in vulnerable patient subsets, including the elderly and patients with significant renal, hepatic or ischemic comorbidity. Data from the Blue Cross Blue Shield of Michigan Cardiovascular consortium have demonstrated a steady linear increase in prasugrel (a third generation thienopyridine antiplatelet agent) prescription following percutaneous coronary intervention.[17] In some cases (28.3%) prasugrel prescription had been inappropriately substituted for clopidogrel and 6–10% of patients prescribed had at least one contraindication to prescription, commonly elderly age.[18]

The data from Michigan are striking given the Trilogy-ACS study has demonstrated no advantage of prasugrel over clopidogrel in the noninvasive medically managed ACS patient.[19] Interestingly, in these early real-world studies of prasugrel prescription there has been no recognition of the potential risk of GIB and no attempt to assess GIB risk factors despite RCT data that demonstrate prasugrel and ticagrelor are associated with a 32%[20] and 19%[21] increased risk of bleeding events, respectively, when compared with clopidogrel. In these RCTs the most common site of bleeding was the gastrointestinal tract, with the greatest absolute increase in major bleeding in the elderly.[20,21]

Now, more than ever, a close collaboration between gastroenterologist, cardiologist and internist needs to be encouraged to keep our patients safe from both a cardiac and gastrointestinal standpoint. The challenges inherent to the management of patients who require chronic antithrombotic therapy are real, and have prompted a call for the development of new clinical paradigms that integrate cardiology and gastroenterological clinical science to develop collaborative 'cardiogastroenterology' clinical paradigms.[9,22] Concerned national gastroenterology and cardiology societies have published multidisciplinary guidance for clinicians who manage these patients

Cardiogastroenterology: Gastrointestinal Bleeding Risk Minimization Strategies

Many knowledge gaps exist and significant research must be conducted to refine cardiogastroenterology clinical paradigms. Until these paradigms reach maturation, there are some basic risk minimization strategies that can be immediately embraced to diminish risk of drug-related GIB in cardiac patients.

1. Use the lowest-dose of ASA possible for cardiac benefit. The CURRENT-OASIS-7 trial has demonstrated that increasing the dose of ASA beyond 81 mg does not confer additional cardioprotective benefit, but does substantially increase the risk of GIB.[26] As the risk of GIB increases with ASA dose escalation, chronic ASA doses greater than 81 mg/day should be avoided. Furthermore, all forms of ASA are associated with an increased risk of GIB; no protection is conferred from enteric or buffered preparations.[25]
2. *H. pylori* should be eradicated if found. Among chronic NSAID users and chronic ASA users, *H. pylori*eradication does reduce the risk of future GIB; especially among patients who have a history of ulcer bleeding.[25]
3. Use CAT with caution. The risk of ASA + thienopyridine +/- anticoagulant therapy is associated with a meaningful and significant risk of UGIB, LGIB and bleeding-related transfusion and hospitalization.[10] Thus, use of combination therapy should only be used when benefits are likely to outweigh the risks.[10,27] It is also important to perform regular, frequent medication reconciliation with patients to guard against polypharmacy contributing to a high-daily dose of antithrombotic. Inadvertent CAT is just as dangerous to the gastrointestinal tract as intentional CAT. Polypharmacy is common among patients more than 65 years, for whom a new drug is prescribed at 75% of ambulatory visits, resulting in 50% of older adults taking up to five drugs and causing adverse effects in 82%.[28]
4. PPI gastroprotection should be provided to individuals at high-risk of bleeding. PPIs are the preferred agents for the therapy and prophylaxis of ASA-associated gastrointestinal injury of the upper gastrointestinal tract.[25] In the COGENT trial, PPIs led to a 66% reduction in UGIB among

patients on dual antiplatelet agents,[29] and have been shown to be cost effective.[30] Similarly, the OBERON trial demonstrated a reduction in the occurrence of endoscopically-confirmed PUD among patients prescribed low-dose ASA and PPI at 40 mg [hazard ratio (HR) 0.18; 95% CI: 0.10–0.37] or 20 mg/day (HR 0.14; 95% CI: 0.07–0.30).[31] PPIs have also been shown to reduce the risk of ASA-induced UGIB to a greater degree than histamine-blockers.[23] Current multidisciplinary guidelines endorse the use of PPI for the gastroprotection of patients at highest risk of GIB. These patients include those with a prior history of GIB and PUD, the elderly and the highly comorbid, and those patients concomitantly prescribed ASA, thienopyridine antiplatelet agents, nonsteroidal (NSAID) agents or anticoagulants.[23] At lesser, and possibly still increased risk include patients with ASA-induced dyspepsia and oral glucocorticoids.[23,25] Nonetheless, data from both the United States and Europe have demonstrated poor adherence to gastroprotection recommendations of ASA and NSAID users,[32,33] highlighting clinical gaps in care which, if corrected, may significantly reduce morbidity and mortality in the cardiac patient.

However, epidemiological and capsule endoscopy studies have demonstrated increased risk of lower gastrointestinal complications and small-bowel mucosal damage among low-dose ASA users.[8] At this time, there is no evidence to suggest a pharmacologic agent can protect against formation of ASA-induced mucosal defects or antithrombotic-related small intestinal or colonic bleeding from preexisting mucosal defects. Until such an agent is developed, the safest strategy is to minimize the dose of ASA to the lowest dose possible (81 mg/day in most patients) and to limit exposure to CAT to the period of time deemed clinically critical.

Conclusion

Knowledge Gaps and Future Research Needs

Clinical scientists in both gastroenterology and cardiology are recognizing the importance of further quantification of patient risk-benefit, individualization of care and inclusion of patient preferences and values when prescribing complex antithrombotic medications. Maturation of clinical paradigms for optimal cardiogastroenterological care requires additional clinical research in this area. Immediate knowledge gaps that need to be addressed include the necessity for better characterized risk-benefit data in special GIB patients who are prescribed these drugs. The elderly and those patients with renal dysfunction are at particular risk for NOAC bleeding given the majority of agents are dependent on renal excretion; thus, they are intrinsically a group at higher risk of GIB.[11] Also needed are studies to explore the comparative safety of NOAC drugs on the gastrointestinal tract and will assist in delineating true incidence of UGIB and LGIB events.

The emerging evidence that these drugs (traditional or new) when combined in dual and triple combinations are associated with a clinically significant and meaningful risk, could be further minimized with greater attention to individualizing treatment regimens and greater awareness of pharmacogenetic factors that may influence an individual's ability to metabolize these agents. These factors include potential new and unexplored drug–drug interactions involving third generation thienopyridine drugs (such as prasugrel and ticagrelor) that occur when combined with NOAC agents (such as dabigatran, rivaroxaban and apixaban).

Ongoing pharmacogenetic clinical trials and improvements in point-of-care genetic testing will assist clinicians in performing real-time assessments of future risk-benefit when prescribing CAT. However, for genetic testing to be relevant to a busy clinician, pragmatic and rational clinical paradigms will need to be developed that incorporate point-of-care pharmacogenetic testing in a busy clinical environment. Finally, improved efforts at risk stratification will assist both cardiologists and gastroenterologists to work together to articulate risk-benefit for their patients and in this fashion, include the patients in shared decision-making regarding complex antithrombotic prescription.

References

How to cite this article
Sharma J. and Sharma P. (2015). Gastrointestinal Bleeding in Cardiac Patients. *Int. J. Pharm. Life Sci.*, 6(1):4209-4213**.**
Source of Support: Nil; Conflict of Interest: None declared

Received: 19.11.14; Revised: 20.12.14; Accepted:29.12.14

© Sakun Publishing House (SPH): IJPLS