Risk of Upper Gastrointestinal Bleeding From Different Drug Combinations

Gastroenterology

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Abstract and Introduction

Abstract

Background & Aims Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin increases the risk of upper gastrointestinal bleeding (UGIB). Guidelines suggest avoiding certain drug combinations, yet little is known about the magnitude of their interactions. We estimated the risk of UGIB during concomitant use of nonselective (ns)NSAIDs, cyclooxygenase -2 selective inhibitors (COX-2 inhibitors), and low-dose aspirin with other drugs.

Methods We performed a case series analysis of data from 114,835 patients with UGIB (930,888 person-years of follow-up) identified from 7 population-based health care databases (approximately 20 million subjects). Each patient served as his or her own control. Drug exposure was determined based on prescriptions of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin, alone and in combination with other drugs that affect the risk of UGIB. We measured relative risk (incidence rate ratio [IRR] during drug exposure vs nonexposure) and excess risk due to concomitant drug exposure (relative excess risk due to interaction [RERI]).

Results Monotherapy with nsNSAIDs increased the risk of diagnosis of UGIB (IRR, 4.3) to a greater extent than monotherapy with COX-2 inhibitors (IRR, 2.9) or low-dose aspirin (IRR, 3.1). Combination therapy generally increased the risk of UGIB; concomitant nsNSAID and corticosteroid therapies increased the IRR to the greatest extent (12.8) and also produced the greatest excess risk (RERI, 5.5). Concomitant use of nsNSAIDs and aldosterone antagonists produced an IRR for UGIB of 11.0 (RERI, 4.5). Excess risk from concomitant use of nsNSAIDs with selective serotonin reuptake inhibitors (SSRIs) was 1.6, whereas that from use of COX-2 inhibitors with SSRIs was 1.9 and that for use of low-dose aspirin with SSRIs was 0.5. Excess risk of concomitant use of nsNSAIDs with anticoagulants was 2.4, of COX-2 inhibitors with anticoagulants was 0.1, and of low-dose aspirin with anticoagulants was 1.9.

Conclusions Based on a case series analysis, concomitant use of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin with SSRIs significantly increases the risk of UGIB. Concomitant use of nsNSAIDs or low-dose aspirin, but not COX-2 inhibitors, with corticosteroids, aldosterone antagonists, or anticoagulants produces significant excess risk of UGIB.

Introduction

Upper gastrointestinal bleeding (UGIB) has a major impact on patients' quality of life and public health care costs.[1] Although great improvements in prevention and treatment of UGIB have been achieved in recent decades, UGIB-related morbidity and mortality remain substantial.[2] Most previous studies have focused on risks associated with use of nonsteroidal anti-inflammatory drugs (NSAIDs), which is one of the most common causes of UGIB. Clinical guidelines therefore recommend preventive strategies for at-risk patients treated with NSAIDs, including coprescription of proton pump inhibitors. Another preventive strategy is use of cyclooxygenase-2 selective inhibitors (COX-2 inhibitors), developed as a safer alternative to nonselective (ns)NSAIDs, especially among high-risk patients.[3]

Use of low-dose aspirin is considered the standard of care for cardiovascular prevention. However, low-dose aspirin is also known to increase the risk of UGIB.[4] The relative risk of UGIB associated with current use of low-dose aspirin compared with no use ranges from 1.6 to 4.0.[4–6] Thus, coprescription of gastroprotective agents (GPAs) is also recommended for at-risk patients treated with low-dose aspirin as a key strategy to minimize upper gastrointestinal