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

events.[7] Adherence to preventive strategies in patients treated with low-dose aspirin is especially important given that an estimated 20% of these patients will also use NSAIDs and approximately 35% of the elderly population regularly uses low-dose aspirin.[7]

Clinical guidelines suggest avoiding use of certain drugs in combination with nsNSAIDs as well as COX-2 inhibitors; these drugs include corticosteroids, anticoagulants, selective serotonin reuptake inhibitors (SSRIs), and antiplatelets.[8] However, the concurrent use of NSAIDs and these other drugs has not been widely studied, and it remains unknown if, and to what extent, combinations of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin with specific other drug groups exert synergistic effects on the risk of UGIB.

Understanding drug synergism is important in developing strategies to minimize the risk of UGIB, particularly in elderly patients who are at high risk for UGIB and are likely to use multiple drugs.[9,10] Therefore, we aimed to estimate the magnitude of interaction between nsNSAIDs, COX-2 inhibitors, or low-dose aspirin and specific drug groups reported to affect the risk of diagnosed UGIB.

Patients and Methods

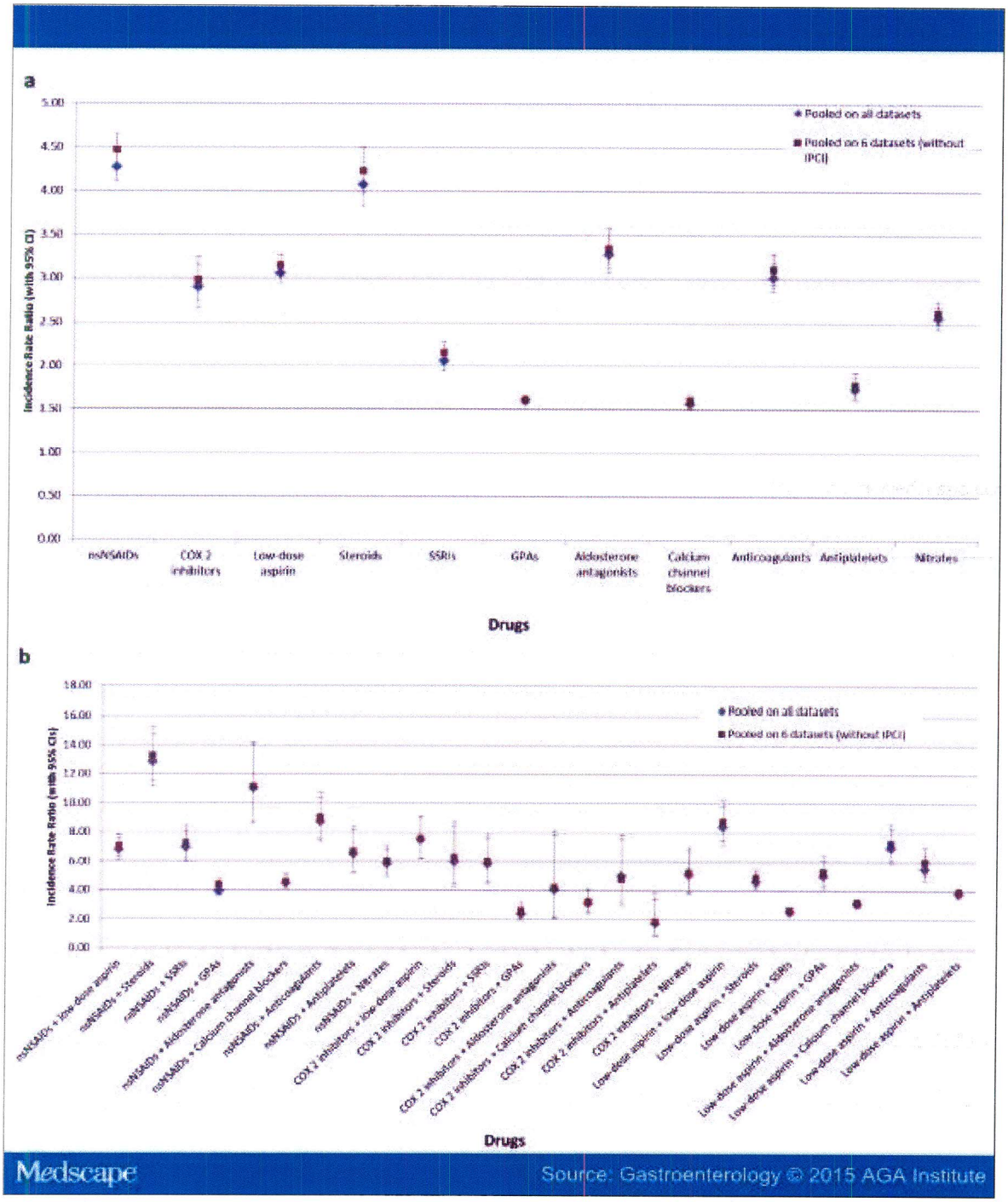
Data Sources

Data were obtained from a network of 7 electronic health record (EHR) databases from 3 countries. The EU-ADR Project (Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge) has successfully established a platform that integrates data from various repositories of European EHRs for evaluation of drug safety.[11]

We analyzed data from 3 primary care databases (Integrated Primary Care Information [IPCI, The Netherlands]; Health Search/CSD Longitudinal Patient Database [HSD, Italy]; and Pedianet [Italy]) and 4 administrative/claims databases (Aarhus University Hospital Database [Aarhus, Denmark], PHARMO Institute [PHARMO, The Netherlands], and the regional databases of Lombardy [UNIMIB, Italy] and Tuscany [ARS, Italy]). The characteristics and study periods of the databases are shown in . All of these databases have been extensively used in epidemiological studies.[11–14] Subjects can enter and may also leave the database at any time for several reasons (eg, death, moving out of the region, leave of practice). The primary care databases capture all prescriptions from general practitioners and some from secondary care (eg, repeat prescriptions). The study protocol was approved by the review board for all databases.

Table 1. Database Characteristics and Number of Cases of UGIB per Database

Database (country)	No. of cases of UGIB	Total person-time of follow-up (*person-years*)	Type of database	Disease coding system	Drug coding system	Study period	Relative contribution of UGIB cases to data set pooled at patient level (%)	PPV o codes used t identif UGIB i databas
Aarhus (Denmark)	11,923	75,963	Administrative/claims	ICD-10	ATC	1999–2008	10.4	77% (95 CI, 69–8
ARS (Italy)	11,519	49,417	Administrative/claims	ICD-9-CM	ATC	2002–2008	10.0	72% (95 CI, 65–7
UNIMIB (Italy)	69,384	680,254	Administrative/claims	ICD-9-CM	ATC	2003–2006	60.4	72% (95 CI, 65–78)[b]



Supplementary Figure 4.

Observed IRRs (with 95% CIs) of drug monotherapy for main analysis and sensitivity analyses excluding IPCI.

Discussion

We determined the magnitude of increased risk of diagnosed UGIB when nsNSAIDs, COX-2 inhibitors, and low-dose aspirin were combined with specific drug classes that may be independently associated with diagnosed UGIB. Although it may seem reasonable to assume synergistic effects with concurrent use of drugs that independently increase risk, these effects have rarely been investigated. To study the risk of diagnosed UGIB during use of specific drug

combinations, it is essential to have a large number of data and an efficient study design. For this study, we used data from a huge network of European electronic health care databases, representing more than 20 million subjects. In addition, the SCCS is a suitable and efficient method to address the question of excess risk of UGIB with drug combinations while at the same time controlling for time-fixed confounding factors as well as confounding by indication. We observed that, overall, the risk of UGIB during concomitant use of drugs was significantly higher compared with what would have been expected based on the sum of the risk of the individual drugs. The magnitude of statistical additive interaction, which may be seen as a surrogate measure for biological synergism, was highest for the combination of nsNSAIDs with corticosteroids and the combination of nsNSAIDs with aldosterone antagonists. In line with previous studies, we observed that the risk of nsNSAID monotherapy was higher than that of monotherapy with low-dose aspirin or COX-2 inhibitors.[4,24] The risk of UGIB was always higher for drug combinations with nsNSAIDs than that for low-dose aspirin or COX-2 inhibitors.

Given that nsNSAIDs, COX-2 inhibitors, and low-dose aspirin are commonly used by elderly patients, with a self-reported prevalence of 35%,[7] the observed risks in the current study emphasize the substantial risk of use of nsNSAIDs, COX-2 inhibitors, and low-dose aspirin in the general population. This is especially true considering that elderly patients are inherently at higher risk due to physiological aging mechanisms.[10,34]

Corticosteroids

Interestingly, we observed that the risk of diagnosed UGIB with use of corticosteroid monotherapy was of the same magnitude as that with nsNSAID monotherapy. Previous studies have shown inconsistent results with respect to risk of UGIB with corticosteroids.[20,21,23] Because nsNSAIDs are known to pose a greater risk of inducing upper gastrointestinal ulcers compared with COX-2 inhibitors, interaction between corticosteroids and nsNSAIDs, but not with COX-2 inhibitors, was expected.[35] The suggested pathophysiological mechanism behind this increased risk for corticosteroids is inhibition of ulcer healing.[39] Previous studies estimated the magnitude of this risk to range from 9-fold to 12-fold,[21,22–24,35] although drug interaction between corticosteroids and nsNSAIDs was not consistently observed.[23] Aside from the small numbers of concomitant users of nsNSAIDs and corticosteroids in previous studies,[20–22,24] there were also differences in outcome definitions and reference categories used (varying from no drug use in the past 7 days[23] to 180 days[24]). According to guidelines, corticosteroids should be considered an independent risk factor for UGIB and gastroprotective measures should be prescribed to patients treated with corticosteroids.[8] To translate the observed risks to the general population, we estimated the PAR due to drug use. The PAR was 6.4% for concurrent use of nsNSAIDs and corticosteroids, 11.8% for nsNSAID monotherapy, and 10.4% for corticosteroid monotherapy. This implies that the proportion of UGIB in the general population attributable to the previously mentioned therapies was high, given the assumption that the association between drug use and occurrence of UGIB is causal. Although this can be reduced by correct use of gastroprotection, future studies should investigate the risk of a combination of corticosteroids and nsNSAIDs with GPAs compared with a combination of corticosteroids and COX-2 inhibitors.

SSRIs

SSRIs showed statistically significant interaction with nsNSAIDs and COX-2 inhibitors but not with low-dose aspirin. From a biological point of view, this interaction seems plausible because SSRIs decrease the serotonin level, resulting in impaired thrombocyte aggregation and an increased risk of bleeding in general, including UGIB. Based on this mechanism, NSAIDs, and low-dose aspirin to a lesser extent,[36,37] are suspected to produce synergism with SSRIs. Although previous studies report an increased risk between 2.6-fold and 16-fold for UGIB with use of SSRIs and NSAIDs when compared with drug monotherapy,[36–38] others could not show interaction.[25,38] However, these were not performed primarily on NSAID users,[37] did not control for important confounders,[36,37] and did not create mutually exclusive drug exposure groups.[36]

Aldosterone Antagonists

The risk of aldosterone antagonists concurrently used with nsNSAIDs was higher than when used with low-dose aspirin or COX-2 inhibitors. Earlier, case reports indicated a possible association between aldosterone antagonists and UGIB or

UGI ulcers.[39] More recently, case-control studies confirmed this association.[13,27] The potential mechanism may be related to impaired healing of gastric and duodenal erosions due to inhibition of fibrous tissue formation.[13]

Anticoagulants and Antiplatelets

Use of anticoagulants is an acknowledged risk factor for UGIB, with previous studies showing risks from 5.3-fold to 6.5-fold for concomitant use of anticoagulants with low-dose aspirin,[18,30] 4.6-fold with COX-2 inhibitors,[18] and up to 19-fold with nsNSAIDs.[4] In the current study, anticoagulants showed a higher risk when combined with low-dose aspirin than with nsNSAIDs or COX-2 inhibitors. The difference between these findings and previous studies may rely on less stringent control for confounders in previous studies than in the current study; furthermore, with the SCCS, all within-person confounders that are fixed over time are immediately dealt with. In line with others, concomitant use of low-dose aspirin eliminates the presumed benefit of COX-2 inhibitors over nsNSAIDs on the risk of upper gastrointestinal adverse events.[4,40–42]

GPAs

The increased risk of diagnosed UGIB observed with the concomitant use of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin with GPAs seems counterintuitive; however, no interaction was observed for any of these drug combinations. The increased risk is thus more likely explained by the phenomenon of "channeling," in which high-risk patients receive concurrent prescriptions for GPAs whereas low-risk patients do not. Another explanation is protopathic bias, because GPAs might be given as treatment for first symptoms of UGIB.[43]

Age-related COX Enzyme Selectivity

As expected, the risk of diagnosed UGIB with use of the drugs of interest (monotherapy), except antiplatelets, was lower for subjects younger than 60 years of age than for subjects older than 60 years of age. Surprisingly, the difference in risk between younger and older subjects was larger for drug combinations with COX-2 inhibitors than for combinations with nsNSAIDs. Application of a cutoff level of 70 years of age did not yield different results. However, using an age cutoff of 70 years showed excess risk for the combination of COX-2 inhibitors and corticosteroids, whereas this was not present with an age cutoff of 60 years. In elderly subjects, prostaglandin levels decreased due to decreased conversion of arachidonic acid to prostaglandin, resulting in an increased risk of UGIB. This partially accounts for the recommendation to use gastroprotective measures in elderly patients.[8] We hypothesize that COX enzyme selectivity with aging might explain the difference in drug interaction between nsNSAIDs and COX-2 inhibitors. In animal studies, older rats expressed different COX enzyme mRNA levels than younger rats and an impaired response of prostaglandin synthesis to irritants with older age was shown.[9] In humans, higher basal acid output in the stomach among elderly patients[34] results in lower mucosal prostaglandin concentrations in the stomach and duodenum.[44] However, these observations were related to the COX-1 enzyme and do not explain our findings. Because the SCCS, by definition, controls for confounders fixed within person and the baseline risk, this also does not explain the difference between younger and older subjects for COX-2 inhibitor combinations in the current study. Future studies are needed to elucidate these findings.

Strengths and Limitations

A major strength of the current study is that while previous studies reported data from single centers[4] or single databases,[9,13,18,20,21,22,25,30,36–38] we performed a multidatabase study to increase the power for studying the risk of UGIB due to drug synergism of relatively uncommon drug combinations. Additionally, we specifically looked at drug combinations of low-dose aspirin, nsNSAIDs, and COX-2 inhibitors separately.[14]

However, we acknowledge the following limitations. A key assumption of the SCCS is that the exposure distribution within the observation period and the observation period itself must be independent of the time of the event. This assumption could have been violated, because the standard of care considers use of an nsNSAID without gastroprotection as relatively contraindicated after occurrence of UGIB. However, sensitivity analyses involving truncation of follow-up at the time of the event showed that drug exposure of nsNSAIDs did not change after the event (ie, results obtained were similar to those from the original analysis), meaning that confounding by contraindication was unlikely to explain the

findings (Supplementary Figure 2). The health condition of a subject may vary over time at all phases of follow-up. Nevertheless, many chronic conditions, such as type 2 diabetes mellitus, hypertension, and peripheral vascular disease, are relatively stable diseases and vary little over time. We have no reason to believe that this will influence the estimates. The sensitivity analysis adjusting for acute myocardial infarction and anaphylactic shock did not yield different estimates as compared with the main analysis (Supplementary Figure 3). In addition, the age of a subject increases during follow-up, and given that older subjects are at higher risk than when at a younger age, we also adjusted for age in the analysis. Residual confounding due to an underlying clinical condition that led to a drug prescription, although unlikely, cannot be ruled out.

Misclassification of exposure time of NSAIDs could have occurred, because NSAIDs are often used intermittently rather than continuously, although this is probably true more for over-the-counter use of NSAIDs. Over-the-counter use of NSAIDs is not captured in EHR databases and could have led to a potential underestimation of use. However, the proportion of NSAIDs used over the counter is limited given that prescribed NSAIDs are reimbursed whereas over-the-counter drugs are not. Although information on drug use differed between dispensing and prescribing data, patterns of use of NSAID classes varied among different countries but were similar among different databases in the same country.[11] In addition, we defined nonexposure as no use of any of the drugs of interest instead of no use of any drug. We mitigated misclassification of nonexposure by restricting the analysis to drugs that have been reported to significantly increase or decrease the risk of UGIB. We used a rather broad definition of UGIB, including all gastroduodenal ulcers and hemorrhages, which may have led to less severe cases of UGIB in the primary care databases compared with administrative databases. A validation study was performed in 4 databases. For this purpose, a sample of UGIB cases was manually validated by medical chart review to characterize and document any outcome misclassification related to drug-associated UGIB. This showed that misclassification was uncommon and did not affect the magnitude of risk estimates.[17] Second, when excluding the data set with the lowest PPV for diagnosis of UGIB in the current study, the estimates were not different from the main analysis. In addition, incidence rates of UGIB in these databases did not differ substantially across European countries and are in accordance with the literature.[11] Variceal bleeding was not included as part of the definition of UGIB. However, we cannot rule out that variceal bleeding may have been wrongly coded as a code more specific for UGIB than variceal bleeding.

Nevertheless, nondifferential misclassification cannot be ruled out and may have resulted in an underestimation of the true estimates. Finally, we did not take any carryover effect or dose of drug exposure into account, which potentially limits the generalizability concerning causality of the associations.

The SCCS assumes that observation periods should be independent of event times, which may be violated if subjects die quickly after the event. By applying an alternative method[45] in one database, taking this assumption into account by weighting the post-event periods, the estimates remained within the 95% confidence limits of the original analysis.

When estimating the magnitude of interaction, the presence and direction depend on the scale used: either additive or multiplicative interaction. In the current study, multiplicative interaction was only observed for the combination of low-dose aspirin and antiplatelets. However, statistical interaction does not directly imply biological interaction.[32]

In conclusion, concomitant use of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin with SSRIs is associated with a significantly increased risk of diagnosed UGIB. Concomitant use of nsNSAIDs or low-dose aspirin, but not COX-2 inhibitors, with corticosteroids, aldosterone antagonists, or anticoagulants was associated with an increased and excess risk of UGIB. These findings may help clinicians in tailoring therapy to minimize UGIB adverse events and are especially valuable in elderly patients who are likely to use multiple drugs concurrently.

References

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