Drug–drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding

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Abstract

Background: Anticoagulants and antiplatelet drugs (e.g., warfarin, clopidogrel and acetylsalicylic acid) are key therapeutic agents in the treatment of cardiovascular diseases. However, drug–drug interactions may lead to a greatly increased risk of gastrointestinal bleeding when these drugs are combined. We assessed whether antithrombotic drug combinations increased the risk of such bleeding in a general practice population.

Methods: We conducted a population-based, retrospective case–control study using records in the United Kingdom General Practice Research Database from 2000 through 2005. Cases were identified as patients over 18 years of age with a first-ever diagnosis of gastrointestinal bleeding. They were matched with controls by physician practice, patient age and index date (date of diagnosis of bleeding). All eligible patients had to have at least 3 years of follow-up data in the database. Drug exposure was considered to be any prescription issued in the 90 days before the index date.

Results: There were 4028 cases with a diagnosis of gastrointestinal bleeding and 40 171 matched controls. The prescribing of acetylsalicylic acid with either clopidogrel (adjusted rate ratio [RR] 3.90, 95% confidence interval [CI] 2.78–5.47) or warfarin (adjusted RR 6.48, 95% CI 4.25–9.87) was associated with a greater risk of gastrointestinal bleeding than that observed with each drug alone. The same was true when a nonsteroidal anti-inflammatory drug was combined with either clopidogrel (adjusted RR 2.93, 95% CI 1.74–4.93) or warfarin (RR 4.60, 95% CI 2.77–7.64).

Interpretation: Drug combinations involving antiplatelets and anticoagulants are associated with a high risk of gastrointestinal bleeding beyond that associated with each drug used alone. Physicians should be aware of these risks to better assess their patients' therapeutic risk–benefit profiles.

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Antithrombotic drugs are used for the prevention and treatment of cardiovascular disorders.[1,2] However, co-prescribing these drugs or prescribing them with others such as nonsteroidal anti-inflammatory drugs can create important drug–drug interactions that can lead to an increased risk of gastrointestinal bleeding.[3–6] This increased risk may be much greater than the product of the risks associated with each drug. We conducted this study to assess whether an increased risk of gastrointestinal bleeding due to drug–drug interactions between antithrombotic medications existed in a general practice population.

Methods

Study design

We conducted a population-based, retrospective case–control study using records in the United Kingdom (UK) General Practice Research Database from Jan. 1, 2000, through Dec. 31, 2005. This is a well-validated database of a network of more than 400 general practices in the United Kingdom[6–8] that has been widely used for pharmacoepidemiology research, including studies of gastrointestinal bleeding.[9,10] The electronic medical records in the UK General Practice Research Database include all important medical events and all prescriptions, since the general practitioner is the centre of health care in the United Kingdom. As a result, the database is a reliable source of information to study drug effects in a clinical setting.[6–8]

We defined a case as any patient 18 years or older whose record in the database contained a first-ever entry of a computerized code for gastrointestinal bleeding. The date of diagnosis was taken as the index date for the case. Using incidence-density sampling, we selected up to 10 controls for every case in the database matched by practice, patient age (± 2 years) and index date. To permit a full assessment of patient comorbidity and lifestyle information, all patients had to have medical records with at least 3 years of data recorded before the index date.

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Table 1: Characteristics of patients with upper gastrointestinal bleeding (cases) and matched controls

Characteristic	Group; no. (%) of patients* Cases *n = 4 028*	Controls *n = 40 171*
Age, yr		
Mean (SD)	69.3 (17.6)	69.1 (17.7)
Range	18–104	18–105
Male sex	2 171 (53.9)	17 237 (42.9)
Female sex	1 857 (46.1)	22 934 (57.1)
Body mass index, kg/m^2		
< 18	105 (2.6)	690 (1.7)
18–29.9	2 289 (56.8)	23 636 (58.8)
30–39.9	514 (12.8)	4 780 (11.9)
≥ 40	56 (1.4)	399 (1.0)
Not recorded	1 064 (26.4)	10 666 (26.6)
Blood pressure		
High	959 (23.8)	8 848 (22.0)
Borderline	978 (24.3)	8 264 (20.6)
Normal	741 (18.4)	5 518 (13.7)
No reading in past year	1 350 (33.5)	17 541 (43.7)
Smoking status		
Smoker	1 797 (44.6)	13 780 (34.3)
Nonsmoker	1 763 (43.8)	20 702 (51.5)
Not recorded	468 (11.6)	5 689 (14.2)
Heavy alcohol use	395 (9.8)	791 (2.0)
Comorbid condition†		
Acid reflux disease	431 (10.7)	3 321 (8.3)
Peptic ulcer	76 (1.9)	403 (1.0)
Helicobacter pylori infection	56 (1.4)	228 (0.6)
Pulmonary embolism	89 (2.2)	410 (1.0)
Deep-vein thrombosis	139 (3.5)	907 (2.3)
Myocardial infarction	358 (8.9)	2 014 (5.0)
Angina	672 (16.7)	4 477 (11.1)
Stroke	329 (8.2)	1 489 (3.7)
Atrial fibrillation	536 (13.3)	3 362 (8.4)
Congestive heart failure	472 (11.7)	2 290 (5.7)
Rheumatoid arthritis	101 (2.5)	616 (1.5)
Other arthritis	1 252 (31.1)	10 841 (27.0)
Diabetes	512 (12.7)	3 204 (8.0)
Cancer	143 (3.6)	852 (2.1)
Dementia	171 (4.2)	1 029 (2.6)
Liver failure	89 (2.2)	62 (0.2)
Renal failure	125 (3.1)	490 (1.2)
Chronic obstructive pulmonary disease	354 (8.8)	1 875 (4.7)
Drug use other than NSAID or antithrombotic‡		
Antibiotic	1 009 (25.0)	5 990 (14.9)
Antidepressant	632 (15.7)	3 702 (9.2)
Corticosteroid	599 (14.9)	4 729 (11.8)
Diuretic	1 370 (34.0)	10 348 (25.8)
H_2 antagonist	268 (6.7)	1 287 (3.2)
Heparin	4 (0.1)	7 (0.02)
Paracetamol	1 336 (33.2)	7 934 (19.8)
Proton pump inhibitor	930 (23.1)	3 985 (9.9)

Note: SD = standard deviation, NSAID = nonsteroidal anti-inflammatory drug.
*Unless stated otherwise.
†Previous history of condition entered in database medical record before the index date (date of first-ever diagnosis of gastrointestinal bleeding).
‡Any prescription issued in the 90 days before the index date.

We obtained ethics approval for this study from the Scientific and Ethical Advisory Group of the UK General Practice Research Database and the McGill University Health Centre Research Ethics Board.

Outcome measures

The primary exposure of interest was the co-prescription of warfarin or clopidogrel with acetylsalicylic acid or a non-acetylsalicylic-acid nonsteroidal anti-inflammatory drug. Non-acetylsalicylic-acid nonsteroidal anti-inflammatory drugs were defined according to the British National Formulary (www.bnf.org), with the vast majority of prescriptions by general practitioners being for naproxen, diclofenac and ibuprofen. (The full list of agents considered is aclofenac, dexketoprofen, diclofenac, diflunisal, etodolac, fenoprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, piroxicam, sulindac, tenoxicam and tiaprofenic acid). The cyclooxygenase-2 selective inhibitors rofecoxib and celecoxib are defined separately from older traditional nonsteroidal anti-inflammatory drugs. Current drug use was defined as a prescription in the 90 days before the index date; this definition was selected to minimize the misclassification of exposure, since it is difficult to estimate durations of warfarin prescriptions, especially because doses of warfarin may change during the course of a prescription according to changes in the patient's international normalized ratio.

Statistical analysis

We used conditional logistic regression analysis to compute odds ratios as an estimate of rate ratios of gastrointestinal bleeding associated with drug exposure. The odds ratio is a valid estimate of the rate ratio because we used incidence-density sampling to select the matched controls.[11,12] We estimated both the main effects and the statistical (multiplicative) interactions using the same statistical model. The drug–drug interaction term shows the excess risk beyond what would have been predicted from the combination of the individual effects of each drug. The adjusted effect of the drug combination is the total risk of the drug combination, including the effect of each agent individually as well as any excess risk due to the combination of the drugs.

We considered as covariates a past history (indicated by the presence in the patient's medical record of at least 1 medical code entered before the index date) of the following conditions: gastroesophageal reflux, peptic ulcer disease, a positive test result for *Helicobacter pylori*, hypertension, liver failure, renal failure, arthritis, diabetes, cancer (any type), chronic obstructive pulmonary disease and dementia (any type). We also considered as covariates the possible indications for warfarin use, including atrial fibrillation, pulmonary embolism, deep-vein thrombosis, congestive heart failure, myocardial infarction, angina and stroke.

We also compared demographic characteristics of the cases and controls, including age, sex, smoking status, body mass index and history of heavy alcohol use (as indicated by database medical codes). A body mass index of less than 18 kg/m^2 was considered to indicate underweight, of more

than 30 kg/m² but less than 40 kg/m² to indicate obesity, and of 40 kg/m² or higher to indicate morbid obesity. A positive history of smoking (current or past) was grouped together as a single smoking variable given the cross-sectional nature of smoking data in the database.

All statistical analyses were adjusted for potential confounders and markers of health status, as measured by prescriptions in the 90 days before the index date or a diagnosis code for comorbid conditions entered in the database any time before the index date, as well as age, sex, smoking status and body mass index. We used indicator variables for missing demographic or lifestyle data to indicate the presence of a missing variable.

Results

The characteristics of the cases and controls are described in Table 1. Known risk factors for gastrointestinal bleeding were found to be important predictors of increased risk, even in the multivariable analysis. These factors were: male sex (adjusted rate ratio [RR] 1.50, 95% confidence interval [CI] 1.40–1.62), heavy alcohol use (adjusted RR 4.00, 95% CI 3.45–4.63), smoking (adjusted RR 1.23, 95% CI 1.15–1.34), acetaminophen (paracetamol) use (adjusted RR 1.47, 95% CI 1.35–1.60) and liver failure (adjusted RR 7.00, 95% CI 4.78–10.27).

The individual and combined effects of the study drugs are shown in Table 2. The top section of the table describes the risk of gastrointestinal bleeding among patients prescribed a single antithrombotic agent. The lower section of the table describes the much higher risk among patients prescribed combinations of these drugs.

In particular, the combined prescription of acetylsalicylic acid with either clopidogrel (adjusted RR 3.90, 95% CI 2.78–5.47) or warfarin (adjusted RR 6.48, 95% CI 4.25–9.87) was associated with a greater risk of gastrointestinal bleeding than that observed with each drug alone. For example, a prescription of acetylsalicylic acid alone was associated with an increased risk of bleeding (adjusted RR 1.39, 95% CI 1.26–1.53), as was a prescription of warfarin alone (adjusted RR 1.94, 95% CI 1.61–2.34); however, the effect of combining these 2 drugs, as shown above, yielded a significant interaction term (RR 2.23, 95% CI 1.46–3.41; Table 2). This interaction term shows the additional risk of gastrointestinal bleeding from a drug–drug interaction between warfarin and acetylsalicylic acid beyond the risks of each agent. The adjusted effect (total risk) of this drug combination was high (RR 6.48, 95% CI 4.25–9.87).

Similar effects were seen among patients prescribed any nonsteroidal anti-inflammatory drug (either a conventional one or a cyclooxygenase-2 selective inhibitor) with either clopidogrel (adjusted RR 2.93, 95% CI 1.74–4.93) or warfarin (adjusted RR 4.60, 95% CI 2.77–7.64).

Table 2: Individual and combined effects of the study drugs on the risk of gastrointestinal bleeding

Drug use	No. (%) of cases *n = 4 028*	No. (%) of controls *n = 40 171*	Rate ratio (95% confidence interval) Crude	Adjusted*
Individual				
None†	2 124 (52.7)	28 264 (70.4)	1.00†	1.00†
Warfarin	281 (7.0)	1 130 (2.8)	2.64 (2.31-3.03)	1.94 (1.61-2.34)
Clopidogrel	160 (4.0)	532 (1.3)	3.16 (2.63-3.79)	1.67 (1.27-2.20)
ASA	1 122 (27.9)	7 350 (18.3)	1.85 (1.71-2.00)	1.39 (1.26-1.53)
NSAID‡	678 (16.8)	3 707 (9.2)	2.02 (1.84-2.21)	1.78 (1.61-1.97)
COX-2 inhibitor	129 (3.2)	630 (1.6)	2.12 (1.74-2.58)	1.64 (1.31-2.06)
Combination			Adjusted interaction term§	Adjusted effect for drug combination¶
None†	2 124 (52.7)	28 264 (70.4)	1.00†	1.00†
Warfarin + ASA	48 (1.2)	82 (0.2)	2.23 (1.46-3.41)	6.48 (4.25-9.87)
Warfarin + NSAID‡	30 (0.7)	53 (0.1)	1.33 (0.78-2.25)	4.79 (2.79-8.21)
Warfarin + COX-2 inhibitor	6 (0.2)	9 (0.0)	1.37 (0.44-4.30)	4.62 (1.48-14.43)
Clopidogrel + ASA	73 (1.8)	133 (0.3)	1.75 (1.17-2.64)	3.90 (2.78-5.47)
Clopidogrel + NSAID‡	22 (0.6)	43 (0.1)	1.04 (0.56-1.93)	2.90 (1.58-5.35)
Clopidogrel + COX-2 inhibitor	9 (0.2)	19 (0.1)	0.98 (0.40-2.44)	2.60 (1.09-6.23)

Note: ASA = acetylsalicylic acid, NSAID = nonsteroidal anti-inflammatory drug, COX-2 = cyclooxygenase-2.
*Adjusted for potential confounders and markers of health status, as measured by prescriptions in the 90 days before the index date or a diagnosis code for comorbid conditions entered in the database record any time before the index date, as well as age, sex, smoking status and body mass index.
†Patients who were exposed to none of the study drugs; these patients constituted the reference group.
‡This class of drugs includes aclofenac, dexketoprofen, diclofenac, diflunisal, etodolac, fenoprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, piroxicam, sulindac, tenoxicam and tiaprofenic acid.
§Estimated additional risk of exposure to the combination of the 2 drugs beyond the risk associated with exposure to each of the drugs individually (the risks of the individual drugs appear in the top half of the table).
¶Estimated total risk of gastrointestinal bleeding for a patient who is prescribed the 2 drugs simultaneously.

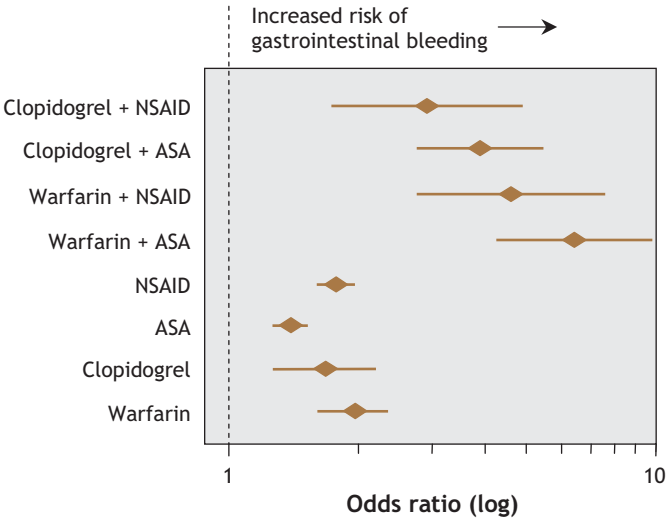

Figure 1: Risk of gastrointestinal bleeding among patients in the United Kingdom General Practice Research Database who were prescribed acetylsalicylic acid (ASA), clopidogrel, warfarin or any type of non-ASA nonsteroidal anti-inflammatory drug (NSAID), either alone or in combination.

A forest plot of the risks of gastrointestinal bleeding associated with the different drugs, alone and in combination, appears in Figure 1.

Interpretation

We found an increased risk of gastrointestinal bleeding associated with drug–drug interactions among patients prescribed antithrombotic agents. The increased risk observed when acetylsalicylic acid was combined with other antithrombotic agents was similar to that seen in other studies.[5] However, our estimates were higher than those derived from the meta-analyses of clinical trials,[1,13] possibly because the monitoring of patients was less strict than that inside the clinical trial environment.[14,15] Indeed, our study was population based, so our statistical inferences should hold in actual clinical settings across a broad sampling of the United Kingdom population.

Our study does have limitations owing to its being based on physician records. Although diagnoses and prescriptions in the UK General Practice Research Database are quite specific, since they are part of patient care management, the database may lack sensitivity because some events or prescriptions could have been missed,[6–8] especially with drugs available over the counter. Our choice of the 90-day exposure period assures that any bias is directed toward the null, since any past user we may have misclassified as a current user should have a risk profile that is more similar to the risk profile of someone not prescribed antithrombotics than to the risk profile of someone with such a drug exposure. There could also have been some degree of confounding by drug indication[16] owing to the choice of nonsteroidal anti-inflammatory drug prescribed, since general practitioners may selectively prescribe a cyclooxygenase-2 selective inhibitor to patients with an increased risk of gastrointestinal bleeding. In addition, our study design does not allow us to make inferences about the appropriateness of the prescriptions. Finally, we lacked the statistical power to look at the risk of gastrointestinal bleeding associated with a 3-way interaction of all antithrombotics.

The low numbers for many of the drug exposures in our study suggest that additional evidence should be gathered from other population databases before definitive conclusions can be reached. This may be especially true for cyclooxygenase-2 selective inhibitors, which have known cardiac and renal risks[17,18] even though the risk of gastrointestinal bleeding associated with them is lower than that associated with conventional nonsteroidal anti-inflammatory drugs.[19] In our results, the risks associated with the cyclooxygenase-2 selective inhibitors and conventional nonsteroidal anti-inflammatory drugs appeared to be comparable.

Our results indicate that physicians need to be aware and weigh the potential risk of gastrointestinal bleeding due to drug–drug interactions with antithrombotic agents against the known therapeutic benefits[13] of these drug combinations.

This article has been peer reviewed.

Competing interests: None declared for Joseph Delaney, Lucie Opatrny or James Brophy. Samy Suissa has received consultancy fees from Sanofi-Aventis for Lantus and leflunomide but not for clopidogrel, which is studied in this paper.

Contributors: All of the authors contributed to the conception and design of the study as well as the acquisition and interpretation of data. Joseph Delaney did the statistical analysis and drafted the manuscript. All of the authors were involved in revising the article for important intellectual content and approved the final version to be published.

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