

Risk factors for gastrointestinal bleeding: a hospital-based case-control study

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Summary

Questions under study/principles: Gastrointestinal (GI) bleeding is a frequent serious adverse drug reaction, potentially causing hospital admission and death. We investigated risk factors for a first-time GI bleeding leading to hospital admission with a focus on drugs and drug-drug interactions (DDIs).

Methods: We conducted a hospital-based case-control study at the Kantonsspital Winterthur, encompassing 74 patients with a first-time GI bleeding in the year 2005 and 148 controls, matched to cases on age, sex and calendar time.

Results: Multivariate models including various drugs and comorbidities revealed a significant risk for GI bleeding for treatment with nonsteroidal antiinflammatory drugs (NSAIDs) (odds ratio [OR] 8.6, 95% confidence interval [CI] 3.1–23) and thrombocyte aggregation inhibitors (OR 2.2, 95% CI 1.1–4.6). Anticoagulation alone in the therapeutic international normal ratio (INR)

range was not associated with bleedings (OR 0.9, 95% CI 0.4–2.3), but INR values ≥ 4 were associated with an increased bleeding risk (OR 13, 95% CI 1.2–150). DDI models yielded increased risk estimates for combined use of NSAID and glucocorticoids (OR 20, 95% CI 1.6–257), and for combined use of oral anticoagulants and NSAIDs (8 cases, 0 controls, crude OR approx. 20).

Conclusion: The findings of this small hospital-based case-control analysis suggest that a first-time GI bleeding is associated with INR values above the therapeutic range, but not with well-controlled oral anticoagulation in the absence of other risk factors such as DDIs. The combinations of glucocorticoids or oral anticoagulants with NSAIDs carry a high risk for GI bleeding.

Key words: gastrointestinal bleeding; case-control study; hospitalization; anticoagulants; nonsteroidal antiinflammatory drug

Introduction

Gastrointestinal (GI) bleeding is one of the most frequent serious adverse drug reactions (ADR) causing hospital admissions [1, 2]. According to Pirmohamed et al., drugs most commonly implicated in causing these admissions included diuretics (27.3%), aspirin (17.8%), nonsteroidal

antiinflammatory drugs (NSAIDs) (11.8%) and warfarin (10.5%). GI bleeding was responsible for more than 50% of all ADRs leading to death [1]. Intake of anticoagulants is commonly recognized as a risk factor for bleeding complications. According to a nationwide study in The Nether-

Abbreviations

ADR	adverse drug reaction
ATC	anatomical therapeutical chemical
BMI	body mass index
CI	confidence interval
DDI	drug-drug interaction
ICD-10	international classification of diseases, 10 th revision

INR	international normalized ratio
NSAID	nonsteroidal antiinflammatory drug
OR	odds ratio
PPI	proton pump inhibitor
TAI	thrombocyte aggregation inhibitor
SSRI	selective serotonin reuptake inhibitor

lands the most frequent ADR-related diagnosis of hospital admissions was bleeding (8.6%), and the drugs most commonly associated with ADR-related hospitalizations were anticoagulants (17.8%) [2]. A Swiss study retrospectively analyzed all hospital admissions during one year and found that about 4% of them were directly related to ADRs. Analyzed by affected organ system, the most frequent ADRs were gastrointestinal complications (33%) caused by platelet aggregation inhibitors, NSAIDs, oral anticoagulants or digoxin. 21% of all ADRs were due to drug-drug interactions (DDIs), whereof the combinations of NSAIDs and oral anticoagulants as well as the combination of platelet aggregation inhibitors and corticosteroids were most frequently observed [3]. Various former studies focused on the interaction between NSAIDs and oral anticoagulants as risk factor for GI bleeding. The short term risk for upper GI bleeding was six times

higher (relative risk 5.8, 95% confidence interval (95% CI) 2.3–14) when anticoagulated patients were also exposed to NSAIDs compared with use of anticoagulants alone [4]. According to Battistella et al., 0.3% of anticoagulated patients (≥ 66 years) were hospitalized with upper GI bleeding per year, and the concomitant intake of NSAIDs was a risk factor for GI bleeding [5]. However, NSAIDs also bear a risk for GI bleeding without concomitant anticoagulant therapy. An observational cohort study showed that the relative risk of upper GI bleeding for elderly users (≥ 66 years) of non-selective NSAIDs was 4.0 (95% CI 2.3–8.5) [6].

The aim of the present hospital-based case-control study was to investigate risk factors for a first-time GI bleeding leading to hospitalization with a special emphasis on the role of drugs and DDIs.

Methods

Study population and data source

The study has been reviewed and accepted by the local Ethics Committee. This retrospective hospital-based case-control study was conducted at the Kantonsspital Winterthur, a 500-bed teaching hospital providing primary and secondary care to a population of approxi-

mately 200 000 inhabitants. Between January and December 2005, patients admitted to the Department of Medicine were eligible to be included in the study.

Information on drugs prescribed at hospital admission (according to the anatomical therapeutical chemical (ATC) classification), demographic information (age and

Table 1
Patient characteristics of cases with first-time gastrointestinal bleeding and matched controls.

		Number of cases (n = 74) (%)	Number of controls (n = 148) (%)
Sex	female	34 (46)	68 (46)
	male	40 (54)	80 (54)
Age	<40	2 (2.7)	4 (2.7)
	40–49	6 (8.1)	12 (8.1)
	50–59	7 (9.5)	13 (8.8)
	60–69	8 (11)	17 (12)
	≥ 70	51 (69)	102 (69)
Body mass index (BMI)	<25 kg/m ²	29 (39)	67 (45)
	25–29.9 kg/m ²	28 (38)	56 (38)
	≥ 30 kg/m ²	12 (16)	22 (15)
	not available	5 (6.8)	3 (2.0)
Co-morbidities (ICD-10 diagnoses)			
Diabetes mellitus	E10–E14	17 (23)	25 (27)
Disorders of lipoprotein metabolism	E78	12 (16)	26 (18)
Hypertensive diseases	I10–I15	13 (18)	12 (8.1)
History of non-bleeding GI ulcer		8 (11)	10 (6.8)
INR ≥ 4		6 (8.1)	2 (1.4)
Death during the hospitalization		4 (5.4)	13 (8.8)
Gastrointestinal bleeding (ICD-10 diagnoses)			
Gastric ulcer, acute with haemorrhage	K25.0	1 (1.4)	–
Gastric ulcer, chronic or unspecified with haemorrhage	K25.4	18 (24)	–
Gastric ulcer, chronic or unspecified with both haemorrhage and perforation	K25.6	2 (2.7)	–
Duodenal ulcer, acute with haemorrhage	K26.0	2 (2.7)	–
Duodenal ulcer, chronic or unspecified with haemorrhage	K26.4	16 (22)	–

(ICD-10: international classification of diseases, 10th revision)

sex), admission date and length of hospital stay, main and additional diagnoses (according to the international classification of diseases, 10th revision (ICD-10) classification), history of non-bleeding GI ulcer, body mass index (BMI) and international normalized ratio (INR) value were obtained from the electronic patient records.

Case definition and ascertainment

Cases were defined as patients older than 18 years, who were hospitalized due to GI bleeding as the main diagnosis. Patients with the following computer-recorded diagnoses (ICD-10) were selected: K25.0, K25.2, K25.4, K25.6, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.4, K28.6, K92.0, K92.1 and K92.2. By reviewing the hospital discharge letters, individuals with a history of GI bleeding prior to the current hospitalization were excluded.

Controls

Controls were patients who were admitted to the Department of Medicine for diseases other than GI bleedings. Among all such potential control patients without current or previous GI bleeding, we identified at random two controls per case, matched on age (± 1 year), sex and calendar time of hospital admission (± 1 month).

Exposure definition

Patients were defined as current users of a drug of interest when, according to the medical history, they were using the drug at the time of the hospital admission. Glucocorticoids included use of betamethasone, cortisone, hydrocortisone, prednisolone, or prednisone, non-steroidal antiinflammatory drugs (NSAIDs) included acemetacin, celecoxib, diclofenac, etodolac, ibuprofen, indometacin, mefenamic acid, or meloxicam, oral antico-

agulants included acenocoumarol or phenprocoumon, selective serotonin reuptake inhibitors (SSRIs) included citalopram, fluoxetine, paroxetine, or sertraline, and thrombocyte aggregation inhibitors included clopidogrel, dipyridamole, high dose aspirin, or low dose aspirin.

Analysis of DDIs

Prescriptions at hospital admission were screened for DDIs potentially causing GI bleeding. As a result of our previous evaluation study of frequently used drug interaction screening programs [7], *Pharmavista* [8] was chosen to check prescriptions for DDIs.

Statistical analysis

We conducted a matched analysis (conditional logistic regression model) using the software program SAS, version 8.02 (SAS Institute, Inc, Cary, NC). Relative risk estimates (odds ratios (ORs)) are presented with 95% CIs. P-values less than 0.05 were considered statistically significant.

For each case and control, the following potential risk factors for GI bleeding were assessed in univariate conditional logistic regression models: BMI (<25, 25–29.9, ≥ 30 kg/m², or unknown), INR value (<2, 2–3.9, ≥ 4 , or unknown), a diagnosis of diabetes mellitus (ICD-10 E10–E14), disorders of lipoprotein metabolism (E78), hypertensive diseases (I10–I15), a history of non-bleeding GI ulcer, use of oral anticoagulants (ATC B01AA), NSAIDs (M01A), glucocorticoids (H02AB), thrombocyte aggregation inhibitors (B01AC), SSRIs (N06AB) and proton pump inhibitors (PPIs) (A02BC).

In a second step, we investigated the role of DDIs and explored whether concomitant use of NSAIDs, glucocorticoids, oral anticoagulants, thrombocyte aggregation inhibitors or SSRIs affected the risk of GI bleeding.

Table 2

Risk estimates for first-time GI-bleeding associated with individual use of drugs and concomitant use of drugs (drug-drug interactions).

	Number of cases (n = 74) (%)	Number of controls (n = 148) (%)	unadjusted OR (95% CI)	adjusted * OR (95% CI)
Any glucocorticoid use	7 (9.5)	6 (4.1)	2.3 (0.8–6.9)	1.7 (0.4–6.2)
Any NSAID use	23 (31)	9 (6.1)	7.0 (2.8–17)	8.6 (3.1–23)
Any oral anticoagulant use	14 (19)	24 (16)	1.2 (0.6–2.5)	0.9 (0.4–2.3)
Any SSRI use	6 (8.1)	5 (3.4)	2.4 (0.7–7.9)	3.3 (0.9–12)
Any TAI use	29 (39)	51 (35)	1.2 (0.7–2.2)	2.2 (1.1–4.6)
Any PPI use	18 (24)	30 (20)	1.3 (0.7–2.5)	1.1 (0.5–2.4)
Hypertensive diseases	13 (18)	12 (8.1)	2.4 (1.0–5.4)	2.2 (0.8–6.0)
INR ≥ 4	6 (8.1)	2 (1.4)	6.9 (1.2–29)	13 (1.2–150)
Non use of NSAIDs and of glucocorticoids	48 (65)	134 (91)	1.0 (ref.)	1.0 (ref.)
NSAID use without glucocorticoid use	19 (26)	8 (5.4)	5.2 (2.2–13)	8.3 (3.0–23)
Glucocorticoid use without NSAID use	3 (4.1)	5 (3.4)	1.2 (0.3–5.0)	1.4 (0.3–7.2)
NSAID use AND glucocorticoid use	4 (5.4)	1 (0.7)	8.0 (0.9–72)	20 (1.6–257)
Non use of NSAIDs and oral anticoagulants	45 (61)	115 (78)	1.0 (ref.)	1.0 (ref.)
NSAID use without oral anticoagulant use	15 (20)	9 (6.1)	3.9 (1.6–9.7)	5.1 (1.8–14)
Oral anticoagulant use without NSAID use	6 (8.1)	24 (16)	0.4 (0.2–1.2)	0.5 (0.2–1.7)
NSAID use AND oral anticoagulant use	8 (11)	0 (0.0)	–	–
Non use of TAI and of oral anticoagulants	34 (46)	74 (50)	1.0 (ref.)	1.0 (ref.)
TAI use without oral anticoagulant use	26 (35)	50 (34)	1.1 (0.6–2.0)	1.9 (0.9–4.2)
Oral anticoagulant use without TAI use	11 (15)	23 (16)	1.0 (0.4–2.1)	0.8 (0.3–2.1)
TAI use AND oral anticoagulant use	3 (4.0)	1 (0.7)	6.0 (0.6–56)	5.1 (0.4–64)
Non use of TAI and of SSRIs	41 (55)	93 (63)	1.0 (ref.)	1.0 (ref.)
TAI use without SSRI use	27 (37)	50 (34)	1.1 (0.6–2.0)	2.2 (1.0–4.5)
SSRI use without TAI use	4 (5.4)	4 (2.7)	2.0 (0.5–8.0)	2.6 (0.6–12)
TAI use AND SSRI use	2 (2.7)	1 (0.7)	4.0 (0.4–44)	16 (0.7–400)

* adjusted for glucocorticoids, NSAIDs, oral anticoagulants, SSRIs, TAIs, PPIs and hypertensive diseases

The final multivariate models included use of glucocorticoids, NSAIDs, oral anticoagulants, SSRIs, thrombocyte aggregation inhibitors, PPIs and hypertensive diseases. We evaluated DDIs in separate models in which we classified patients into mutually exclusive groups of non-

users of drug A and B, users of drug A only, users of drug B only, or users of a combination of A and B, and we adjusted these models for all other drugs not involved in a particular DDI of interest.

Results

Characteristics of the patients and dropouts

During the study period January to December 2005, the Kantonsspital Winterthur registered 19385 admissions, of which 24% (4713) were allocated to the Department of Medicine, wherefrom 1.9% (90) due to GI bleeding as the main diagnosis. 16 cases were excluded (15 patients showed evidence for previous GI bleedings, one patient lacked sufficient clinical information). The detailed main diagnoses of the 74 cases and further characteristics of the cases and of the matched controls are displayed in table 1. During hospitalization, 4 (5.4%) cases and 13 (8.8%) controls died.

Multivariate regression models

In the multivariate model, adjusted for the drugs listed above and for hypertensive diseases, use of NSAIDs (adjusted OR 8.6, 95% CI 3.1–23) and use of thrombocyte aggregation inhibitors (adjusted OR 2.2, 95% CI 1.1–4.6) yielded statistically significantly increased risks for GI bleeding (table 2). Furthermore, SSRI use was also associated with an increased bleeding risk, (adjusted OR 3.3, 95% CI 0.9–12). Use of oral anticoagulant drugs alone in the therapeutic INR range was not associated with bleedings (adjusted OR 0.9, 95%

CI 0.4–2.3). However, high INR values ≥ 4 were associated with an increased bleeding risk (adjusted OR 13, 95% CI 1.2–150).

According to the multivariate DDI models, use of NSAIDs alone, use of glucocorticoids alone, or concomitant use NSAIDs and glucocorticoids, as compared to non-use of both NSAIDs and glucocorticoids, yielded adjusted ORs of 8.3 (95% CI 3.0–23), 1.4 (95% CI 0.3–7.2) and 20 (95% CI 1.6–257), respectively. Furthermore, there were 8 cases and 0 controls who concomitantly used NSAIDs and oral anticoagulants. Due to the zero cell, we could not assess an adjusted OR in a multivariate model, but we calculated a crude OR under the assumption that one (instead of 0) control patient used both an NSAID and oral anticoagulation at the time of the hospitalization, which yielded a crude OR of 20. The adjusted relative risk estimates of developing a GI bleeding were also increased for concurrent use of thrombocyte aggregation inhibitors and oral anticoagulants as well as of thrombocyte aggregation inhibitors and SSRIs (without statistical significance), as compared to single use of these drugs. The detailed results from DDI models are displayed in table 2.

Discussion

Almost 2% of all admissions to the Department of Medicine at the Kantonsspital Winterthur were due to GI bleeding. First-time GI bleeding was registered in slightly more male than female patients (54% *vs* 46%). The number of cases increased with age, more than two thirds of all patients admitted with first-time GI bleeding (69%) were at least 70 years old.

Our study suggests that the risk for GI bleeding under treatment with oral anticoagulants alone was not elevated (adjusted OR 0.9, 95% CI 0.4–2.3), if the INR did not exceed 4, and if patients were not exposed to other risk factors. However, an INR value ≥ 4 was associated with an increased GI bleeding risk (adjusted OR 13, 95% CI 1.2–150). This finding is in line with a recent Norwegian study reporting that 74% of patients treated with warfarin had, according to the authors, INR values above the therapeutic range at the time of GI bleeding [9]. According to a meta-

analysis [10], the OR for major bleeds for INR 3 to 4 compared with INR 2 to 3 was 2.3 (95% CI 0.5–10) and did not reach statistical significance. However, the OR for INR >4 compared with the INR 2 to 3 reference group was highly significant (OR 33, 95% CI 9.1–121). Various studies showed that the safety management and monitoring of an oral anticoagulant therapy is a difficult challenge for both patients and physicians. In such studies, the INR values were beyond the therapeutic range in 41 to 57% of the observation period [11–13].

Patients treated with NSAIDs showed a 9-fold risk (adjusted OR 8.6, 95% CI 3.1–23) for hospitalization due to GI bleeding compared to patients without NSAID treatment. The results of two recent cohort studies showed a 3.6-fold and a 5.5-fold higher risk for current NSAID users of developing upper GI bleeding [14, 15]. According to another large case-control study the ORs

ranged from 1.4 for aceclofenac to 25 for ketorolac, suggesting substantial differences between individual NSAIDs [16]. The annual incidence of NSAID-associated GI bleeding was also estimated in prospective outcome studies. Upper GI bleeding occurred in 3 to 4.5% of patients ingesting NSAIDs per year, and serious bleeding episodes due to bleeding of large blood vessel and/or gastric or intestinal perforation in approximately 1.5% [17].

In our study, there was a suggestion that patients with combined use of NSAIDs and glucocorticoids had a higher GI bleeding risk (OR 20, 95% CI 1.6–257) than patients treated with NSAIDs alone (OR 8.3, 95% CI 3.0–23). Similar results were published by Hallas et al. [14] (increase in risk from 5.5 for patients using NSAIDs alone to 10 for patients using NSAIDs and glucocorticoids), by Mellekjaer et al. [15] (increase in risk from 3.6 to 7.4), by Piper et al. [18] (increase in risk from 1.1 to 4.4) and by Weil et al. [19] (increase in risk from 3.8 to 9.0). The combination of NSAIDs with oral anticoagulants is also associated with a higher risk of GI bleeding than use of NSAIDs alone. In the study of Mellekjaer et al. [15], the risk for GI bleeding increased from 3.6 in NSAIDs users to 11.5 for combined use of anticoagulants and NSAIDs. In a cohort study among NSAIDs users (≥ 65 years), the risk for hospitalization due to a bleeding ulcer was 13-fold increased (95% CI 6.3–26) for combined use of anticoagulants and NSAIDs, and 4.0 (95% CI 3.4–4.8) for use of NSAIDs only [20]. In our study, eight patients were exposed to both NSAID and oral anticoagulants, but none in the control group, precluding the adjusted calculation of an OR, but the OR is approximately 20.

We also analyzed concurrent illnesses such as obesity, diabetes mellitus, hypertensive diseases, disorders of lipoprotein metabolism and history of non-bleeding GI ulcer as risk factors for GI bleeding (table 1). Unadjusted conditional regression analyses yielded significant ORs for patients with hypertensive diseases (OR 2.4, 95% CI 1.0–5.4). However, after adjusting for confounders, the risk estimate decreased (adjusted OR 2.2, 95% CI 0.8–6.0), which is in line with the conclusion of the authors of a recent review article who stated that hypertension may not be an independent risk factor for anticoagulant-related bleeding, when other risk factors were controlled for [21]. On the other hand, the presence of co-morbidities in patients with a GI bleeding is associated with an increased mortality [22].

Limitations

Any epidemiologic studies may be subject to limitations such as confounding factors. Our data were retrieved from electronic medical records, with missing values for certain laboratory parameters such as INR, particularly in control patients. In addition, possible diagnosis misclassifi-

cation and incomplete patient records cannot be fully excluded. Recent studies showed discrepancies of up to 40 or 50% of patients' medication when medical records and patient-reported use of drugs were compared [23–25]. For non-prescription NSAIDs, disagreement was found in 74% of patients' medication [25], and a systematic review reported that up to 61% of patients had at least one omission error in prescription medication histories [26]. Therefore bias due to possible underreporting of NSAID use can not be excluded.

No statement about the GI bleeding risk for individual NSAIDs was possible in our study due to the small number of cases. A meta-analysis suggested that ibuprofen, followed by diclofenac bear the lowest risk for GI bleeding. Azapropazone, tolmetin, ketoprofen, and piroxicam ranked highest for risk where indometacin, naproxen, sulindac, and aspirin occupied intermediate positions [27]. According to a case-control study, ketorolac was associated with the highest risk followed by piroxicam, indomethacin, ketoprofen and naproxen. Lower risks were found for aceclofenac, ibuprofen, nimesulide and diclofenac [16].

In our study, doses and durations of exposure to the drugs were not taken into consideration. In previous studies, increasing doses were shown to be a risk factor for upper GI bleeding [16] especially for ibuprofen and naproxen [15].

Finally, the number of cases ($n = 74$) and matched controls ($n = 148$) was rather small. Bias due to sparse matched sets can affect the magnitude of OR estimates, even when there is no confounding, selection bias or measurement error [28].

In conclusion, the results of this small hospital-based case-control analysis suggest that first-time GI bleeding is associated with high INR values, but not necessarily with oral anticoagulation alone if other risk factors such as DDIs are not present. Oral anticoagulants and NSAIDs as well as glucocorticoids and NSAIDs are frequently prescribed concomitantly in daily practice, and our results emphasize the problems related to concomitant use of these drugs. Strategies for reducing GI bleedings include close monitoring of INR values, careful dose adjustment and prescription of drugs with a known and low potential for DDIs.

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