Increased Bleeding Risk With Concurrent Use of Selective Serotonin Reuptake Inhibitors and Coumarins

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Background: Treatment with vitamin K antagonists (coumarins) is associated with an increased risk of bleeding. Because use of selective serotonin reuptake inhibitors (SSRIs) is also associated with an increased risk of bleeding, we assessed the odds ratio (OR) of abnormal bleeding associated with SSRI use in users of the coumarins acenocoumarol or phenprocoumon and compared this with the OR of bleeding as a result of use of nonsteroidal anti-inflammatory drugs.

Methods: We used data from a Dutch linkage system including pharmacy and linked hospitalization records for approximately 2 million subjects to conduct a case-control study in a cohort of new users of coumarins. Cases were patients who were hospitalized having a primary diagnosis of abnormal major bleeding while taking a coumarin and were matched with up to 4 control subjects. Conditional logistic regression analysis was used to determine ORs and 95% confidence intervals (CIs) for the risk of hospitalization because of abnormal bleeding associated with concurrent use of SSRIs or nonsteroidal anti-inflammatory drugs.

Results: We identified 1848 case patients with abnormal bleeding. Users of SSRIs were at significantly increased risk of hospitalization because of nongastrointestinal tract bleeding (hereafter referred to as "nongastrointestinal bleeding") (adjusted OR, 1.7; 95% CI, 1.1-2.5) but not because of gastrointestinal tract bleeding (hereafter referred to as "gastrointestinal bleeding") (adjusted OR, 0.8; 95% CI, 0.4-1.5). Users of nonsteroidal anti-inflammatory drugs had a similar increased risk of nongastrointestinal bleeding (adjusted OR, 1.7; 95% CI, 1.3-2.2), whereas the risk of gastrointestinal bleeding was higher (adjusted OR, 4.6; 95% CI, 3.3-6.5).

Conclusion: In users of coumarins, SSRI usage was associated with increased risk of hospitalization because of nongastrointestinal bleeding but not because of gastrointestinal bleeding.

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COUMARIN ANTICOAGULANTS are effective drugs for prevention and management of thromboembolic diseases. However, their use is complicated by a narrow therapeutic range and their sensitivity to interactions with other drugs.[1,2] Several interactions can result in an increased risk of major bleeding, the main adverse effect of coumarin anticoagulant therapy.[3]

In several population-based studies, a further increase in the risk of major bleeding in users of coumarin anticoagulants has been convincingly demonstrated for other drugs that increase the risk of major bleeding such as nonsteroidal anti-inflammatory drugs (NSAIDs),[4-6] aspirin,[5,6] and glucocorticoids.[5] In several population-based studies, use of selective serotonin reuptake inhibitors (SSRIs) has also been associated with an increased risk of upper gastrointestinal tract bleeding (hereafter referred to as "gastrointestinal bleeding")[7-10] and with abnormal major bleeding in general.[11] These findings suggest a pharmacodynamic interaction between SSRIs and coumarin anticoagulants. For the SSRIs fluoxetine hydrochloride and fluvoxamine maleate, a pharmacokinetic effect might have a contributing role because both drugs have been identified as inhibitors of CYP2C9, the main metabolizing enzyme of the more active (S)-enantiomers of coumarins.[12,13] Despite these theoretical considerations, a recent population-based case-control study did not find an association between SSRI use and an increased risk of hospitalization because of upper gastrointestinal bleeding in users of warfarin sodium.[14] To examine an association between concurrent use of SSRIs and coumarin anticoagulants with all possible major bleeding, we conducted a population-based case-control study in a cohort of users of the coumarin anticoagulants acenocoumarol and phenprocoumon.

STUDY DESIGN AND SETTING

We conducted a case-control study in a cohort of new users of acenocoumarol or phenprocoumon, the 2 coumarin anticoagulants licensed in the Netherlands. We will further designate these drugs as coumarins.

The setting of the study was the PHARMO Record Linkage System (Pharmo Institute, Utrecht, the Netherlands; available at http://www.pharmo.nl). This system includes the demographic details and complete medication histories from community pharmacies for more than 2 million community-dwelling residents of 25 geographic areas in the Netherlands from 1985 to the present further linked to hospital admission records. Because virtually all patients in the Netherlands are registered with a single community pharmacy, pharmacy records are essentially complete insofar as prescription drug use is concerned. For this study, drug prescribing data and hospitalization data were used. Drugs are coded according to the Anatomical Therapeutic Chemical Classification. The hospital admission and discharge codes are coded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification*.

COHORT AND EXPOSURE TO COUMARINS

In the cohort of new users of one of the coumarin anticoagulants, all patients 18 years or older who received a first prescription for a coumarin between January 1, 1991, and December 31, 2004, and who did not have a history of hospital admission because of major bleeding were included. A patient was defined as a new coumarin user if none of these drugs had been dispensed before the first coumarin dispensing in the PHARMO database and if a medication history for at least 1 year before initiation of the coumarin anticoagulant was available. Patients were followed up until hospital admission because of major bleeding, end of data collection, death, or discontinuation of coumarin therapy, whichever occurred first.

Prescriptions for coumarin anticoagulants do not contain information about the dosage, which is variable and frequently adjusted by anticoagulation clinics. As a consequence, duration of coumarin use cannot be calculated from the number of dispensed units and the prescribed dosage. We assumed that treatment was discontinued if more than 180 days elapsed after the last recorded dispensing date of the coumarin. The period of 180 days has been estimated on the basis of experience in daily practice. Coumarin anticoagulants are usually dispensed in large quantities (several hundred defined daily doses) and, because daily doses show a large interindividual variation, 180 days could be an underestimation or an overestimation of the duration of use.

CASES AND CONTROLS

Cases were all patients with a first hospitalization because of abnormal bleeding while being treated with a coumarin. To identify abnormal bleeding, we used *International Classification of Diseases, Ninth Revision, Clinical Modification,* diagnostic codes. The date of first hospitalization because of abnormal bleeding was considered the index date. For each case patient, up to 4 nonhospitalized control subjects were randomly selected from the cohort by risk-set sampling. Control subjects were matched with case patients for sex, age (±5 years), coumarin anticoagulant used (acenocoumarol or phenprocoumon), time since initiation of coumarin therapy (±90 days from dispensing date), and geographic region, and were assigned the same index date as the corresponding case patient.

DEFINITION OF EXPOSURE

We analyzed the following a priori chosen SSRIs: citalopram hydrobromide, escitalopram oxalate, fluvoxamine maleate, fluoxetine hydrochloride, paroxetine hydrochloride, and sertraline hydrochloride. We also assessed whether use of nortriptyline hydrochloride or mirtazapine was associated with abnormal bleeding; both are frequently prescribed antidepressants without a significant affinity for the serotonin transporter.[15] In the PHARMO database, the duration of use of a dispensed drug is calculated by dividing the number of dispensed units by the prescribed number to be used per day. If the duration of use of an antidepressant extended with 10% ended on or beyond the index date, this was considered current use of that antidepressant. If the duration of use extended with 10% from a dispensing date ended within 30 days or more than 30 days before the index date, it was considered recent use or past use, respectively.

POTENTIAL CONFOUNDERS

As confounding comedication, we defined current use of NSAIDs (selective cyclooxygenase 2 inhibitors were excluded), antiplatelet agents (low-dose aspirin, clopidogrel bisulfate, and dipyridamole), glucocorticoids, gastroprotective agents (proton pump inhibitors, histamine 2 receptor antagonists, and misoprostol), established inhibitors of coumarin metabolism[2,16] (amiodarone, allopurinol, benzbromarone, cimetidine, miconazole, fluconazole, and gemfibrozil), established inducers of coumarin metabolism[2] (carbamazepine, phenytoin sodium, phenobarbitone, and rifampicin), and antibiotics (as a proxy for intercurrent infections). For current use of confounding comedication, we used the same definitions as for SSRIs. Any use before the index date of thyroid therapy, antidiabetes drugs, antineoplastic agents, and a combination of either angiotensin-converting enzyme inhibitors or angiotensin II antagonists with loop diuretics were proxies for thyroid diseases, diabetes mellitus, cancers, and heart failure, respectively.

STATISTICAL ANALYSIS

We used conditional logistic regression models on the matched sets to estimate the risk of bleeding associated with current use of SSRIs, expressed as odds ratios (ORs) with 95% confidence intervals (CIs). We also assessed ORs for current use of NSAIDs (selective cyclooxygenase 2 inhibitors excluded) as a positive test of the validity of our data set because these drugs have been strongly associated with an increased risk of major bleeding and severe overanticoagulation in users of coumarins.[4-6,17] When we assessed ORs for NSAIDs, we also adjusted for use of SSRIs, apart from the confounders mentioned in the "Potential Confounders" section.

We stratified our analyses by gastrointestinal bleeding and nongastrointestinal tract bleeding (hereafter referred to as "nongastrointestinal bleeding"). Moreover, we separately analyzed all intracranial bleeding, which is the potentially most disabling category of nongastrointestinal bleeding. We also stratified our analyses by the CYP2C9 inhibiting SSRIs fluoxetine and fluvoxamine, and the other SSRIs.

In sensitivity analyses, we reanalyzed our results on the assumption that coumarin use ended maximally 30, 60, or 90 days (rather than 180 days) after the last dispensing date and for users who received more than 1 prescription for a coumarin anticoagulant. Moreover, we reanalyzed our results for bleeding events that occurred after the first 28 days of coumarin therapy, increasing the chance that patients are more or less stabilized because the initiation phase can be associated with problems of dose finding and severe overanticoagulation. We also ana-

Table 1. Admission Diagnosis in 1848 Patients in a Cohort of Users of Coumarins Hospitalized With a First Major Bleeding Event

Site of Bleeding	No. (%) of Patients
Gastrointestinal tract	605 (32.7)
Upper	537 (29.0)
Lower	68 (3.7)
Nongastrointestinal tract	1243 (67.3)
Intracranial	318 (17.2)
Uterus	131 (7.1)
Urinary tract	115 (6.2)
Joint	34 (1.8)
Eye	20 (1.1)
Nose	161 (8.7)
Other[a]	464 (25.1)

[a] Includes hemoptysis, bleeding complicating a procedure, hemoperitoneum, spontaneous ecchymoses, and bleeding not otherwise specified.

lyzed our data for recent and past use of the examined drugs. All statistical analyses were performed using commercially available software (SPSS version 12; SPSS Inc, Chicago, Illinois).

RESULTS

We identified 70 201 patients who were treated with a coumarin, for a total of 131 707 patient-years. Within this cohort, we identified 2403 cases of first bleeding requiring hospitalization (incidence rate, 1.82 per 100 patient-years). Of these, 555 patients could not be matched to control subjects, leaving 1848 patients available for analyses, who were matched with 5818 control subjects. The median follow-up in patients until bleeding was 220 days (range, 1-4690 days). Gastrointestinal bleeding occurred in 605 patients, and nongastrointestinal bleeding in 1243 patients. The most frequently occurring category was upper gastrointestinal bleeding, followed by intracranial bleeding (**Table 1**). Mean patient age at the index date was 72.7 years, there were more men than women, and almost 90% of the patients used acenocoumarol (**Table 2**).

Users of SSRIs were at significantly increased risk of hospitalization because of nongastrointestinal bleeding (adjusted OR, 1.7; 95% CI, 1.1-2.5) but not because of gastrointestinal bleeding (adjusted OR, 0.8; 95% CI, 0.4-1.5). For gastrointestinal bleeding, we had a power of 51% to assess the same significantly increased OR of 1.7 ($\alpha = .05$) as for nongastrointestinal bleeding, and we could have detected a significantly increased OR of 2.1 ($\beta = .80$). Analysis for only upper gastrointestinal bleeding (537 patients) resulted in almost the same multivariate OR (0.9; 95% CI, 0.4-1.8) as for all gastrointestinal bleeding. For the non-SSRIs nortriptyline and mirtazapine, no increased risk for both categories of major bleeding was found (**Table 3**). As expected, we found that NSAID use was associated with a higher risk of gastrointestinal bleeding than of nongastrointestinal bleeding (Table 3).

Separate analysis for intracranial bleeding resulted in no significantly increased risk for users of SSRIs (adjusted OR, 1.6; 95% CI, 0.7-3.4; $P = .26$) and NSAIDs (ad-justed OR, 1.6; 95% CI, 1.0-2.8; $P = .06$). For SSRIs, the power to find a significantly increased OR of 1.6 ($\alpha = .05$) was 24%, and we could have detected a significantly increased OR of 2.7 ($\beta = .80$). For NSAIDS, the power to find a significantly increased OR of 1.6 was 44%, and we could have detected a significantly increased OR of 2.1 ($\beta = .80$). Point estimates for SSRIs and NSAIDs were similar to those for all nongastrointestinal tract bleeding.

Separate analyses for users of fluoxetine and fluvoxamine and the other SSRIs did not result in essentially different point estimates for nongastrointestinal bleeding (adjusted OR, 1.4; 95% CI, 0.7-2.9, and adjusted OR, 1.8; 95% CI, 1.1-3.0, respectively) or for gastrointestinal bleeding (data not shown). Numbers were too low for a reliable separate analysis for users of SSRIs and phenprocoumon. However, separate analysis for users of acenocoumarol resulted in similar point estimates as for the pooled analysis of users of both coumarins.

Sensitivity analyses did not change our overall results. The point estimates for nongastrointestinal bleeding remained similar if the assumption for the maximum time between last dispensing date of a coumarin and the index date was reduced from 180 days to 90 days (multivariate OR, 2.0; 95% CI, 1.2-3.3 for SSRIs and multivariate OR, 1.8; 95% CI, 1.3-2.3 for NSAIDs; for 997 patients and 2703 controls), 60 days (multivariate OR, 2.0; 95% CI, 1.2-3.5 for SSRIs and multivariate OR, 1.8; 95% CI, 1.3-2.5 for NSAIDs; for 895 patients and 2250 controls), or 30 days (multivariate OR, 1.7; 95% CI, 0.9-3.1 for SSRIs and multivariate OR, 1.9; 95% CI, 1.3-2.7 for NSAIDs; for 752 patients and 1719 controls); if data for only patients who received more than 1 prescription for a coumarin anticoagulant were analyzed (multivariate OR, 1.8; 95% CI, 1.1-2.9 for SSRIs and multivariate OR, 1.8; 95% CI, 1.4-2.4 for NSAIDs; for 1016 patients and 3073 controls); or if only bleeding after the first 28 days was considered (multivariate OR, 1.8; 95% CI, 1.2-2.9 for SSRIs and multivariate OR, 1.7; 95% CI, 1.3-2.3 for NSAIDs; for 1070 patients and 3728 controls). Only if the maximum time between the last dispensing date of the coumarin and the index date was reduced to 30 days was significance lost for the association with SSRIs ($P = .08$). Results for gastrointestinal outcomes did not change with these assumptions (data not shown). Recent and past use of SSRIs and NSAIDs showed an immediate attenuation of the effect on nongastrointestinal bleeding, with risk no longer increased.

COMMENT

The main finding of our study is that SSRI use is associated with an increased risk of hospitalization because of major nongastrointestinal bleeding but not because of gastrointestinal bleeding in users of coumarin anticoagulants. Kurdyak et al[14] examined a possible association between concurrent use of SSRIs and warfarin sodium and major bleeding. Despite several differences between their study and ours, our findings for gastrointestinal bleeding were similar: Kurdyak and colleagues reported a multivariate OR of 1.1 (95% CI, 0.8-1.7) vs an OR of 0.8 (95% CI, 0.4-1.5) in our study. Although there could have been

Table 2. Characteristics, Current Use of Relevant Medication, and Comorbidities in 7666 Patients and Control Subjects

	No. (%)	
Characteristic	**Patients (n=1848)**	**Control Subjects (n=5818)**
Male sex	993 (53.7)	3173 (54.5)
Age at index date, mean (SD), y	72.7 (10.3)	72.9 (9.7)
Acenocoumarol at index date	1628 (88.1)	5302 (91.1)
Selective serotonin reuptake inhibitors	58 (3.1)	116 (2.0)
Nonserotonergic antidepressants: mirtazapine and nortriptyline	3 (0.2)	19 (0.3)
Nonsteroidal anti-inflammatory drugs	222 (12.0)	299 (5.1)
Antiplatelet agents: aspirin, clopidogrel, and dipyridamole	227 (12.3)	514 (8.8)
Glucocorticoids	113 (6.1)	176 (3.0)
Gastroprotective agents: proton pump inhibitors, histamine 2 receptor antagonists, and misoprostol	313 (16.9)	703 (12.1)
Coumarin metabolism inhibitors: amiodarone, allopurinol, benzbromarone, cimetidine, miconazole, fluconazole, and gemfibrozil	153 (8.3)	385 (6.6)
Coumarin metabolism inducers: carbamazepine, phenytoin, phenobarbitone, and rifampicin	21 (1.1)	66 (1.1)
Antibiotics	148 (8.0)	124 (2.1)
Diabetes mellitus	334 (18.1)	869 (14.9)
Thyroid disorders	104 (5.6)	336 (5.8)
Heart failure	581 (31.4)	1507 (25.9)
Cancers	38 (2.1)	91 (1.6)

Table 3. Association Between Current Use of Antidepressants and NSAIDs and Hospitalization Because of Gastrointestinal and Nongastrointestinal Tract Bleeding

	No. (%)							
	Gastrointestinal Tract Bleeding				**Nongastrointestinal Tract Bleeding**			
Drugs	**Patients (n=605)**	**Control Subjects (n=1914)**	**Univariate OR (95% CI)**	**Multivariate OR[a] (95% CI)**	**Patients (n=1243)**	**Control Subjects (n=3904)**	**Univariate OR (95% CI)**	**Multivariate OR[b] (95% CI)**
SSRIs	15 (2.5)	42 (2.2)	1.1 (0.6-2.0)	0.8 (0.4-1.5)	43 (3.5)	74 (1.9)	1.8 (1.2-2.6)	1.7 (1.1-2.5)
Non-SSRIs	0	9 (0.5)	NA	NA	3 (0.2)	10 (0.3)	1.2 (0.3-4.5)	1.1 (0.3-4.0)
NSAIDs	110 (18.2)	86 (4.5)	4.6 (3.3-6.4)	4.6 (3.3-6.5)	112 (9.0)	213 (5.5)	1.8 (1.4-2.2)	1.7 (1.3-2.2)

Abbreviations: CI, confidence interval; NA, data not available; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; SSRIs, selective serotonin reuptake inhibitors.

[a] In the multivariate analysis, the following factors were included: current use of SSRIs, NSAIDs, antiplatelet agents, antibiotics, glucocorticoids, gastroprotective agents (proton pump inhibitors, histamine 2 receptor antagonists, and misoprostol), inhibitors and inducers of coumarin metabolism, and the comorbidities diabetes mellitus, thyroid disorders, heart failure, and cancers.

[b] In the multivariate analysis, the same factors were included as for gastrointestinal tract bleeding except gastroprotective agents.

a power problem, the consistency of the findings of both studies strongly suggests that SSRIs do not increase the risk of gastrointestinal bleeding in users of coumarins.

We found a substantially increased risk of nongastrointestinal bleeding in current users of SSRIs. This apparently different effect of SSRIs on gastrointestinal and nongastrointestinal bleeding in users of coumarins was unexpected. We found that SSRI use seems to be associated with an increased risk of nongastrointestinal bleeding to the same extent as use of NSAIDs. Whereas there is an obvious difference for gastrointestinal bleeding, NSAID use is associated with a markedly increased risk, but SSRI use has no effect at all.

In users of coumarins with upper gastrointestinal bleeding, underlying known or previously unknown lesions have been identified in as many as 70% of patients.[18] This makes a pharmacodynamic interaction between coumarins and NSAIDs conceivable, and an association be-

tween NSAID use and increased bleeding risk in users of coumarins has been convincingly demonstrated in several population-based observational studies.[4,5,19] If SSRI use is associated with an increased risk of upper gastrointestinal bleeding in users of coumarins, it is probably not a consequence of a gastrointestinal toxic reaction but of decreased platelet aggregation, an effect that has been demonstrated for all SSRIs in patients with depression and in healthy control subjects.[20] Although several population-based observational studies demonstrated an association between use of SSRIs and upper gastrointestinal bleeding[7,8,10,21] or upper and lower gastrointestinal bleeding,[9] in a recent systematic review it was concluded that the overall evidence for such an association is weak,[22] suggesting that SSRIs precipitate bleeding primarily in patients with hemostatic defects or in patients who are taking drugs that cause gastrointestinal injury, such as NSAIDs. This last assertion is supported by the

finding in several studies[7,9,10] of a synergistically increased risk of upper gastrointestinal bleeding with concurrent use of SSRIs and NSAIDs as opposed to separate use of SSRIs and NSAIDs. A possible explanation of this synergism, apart from the toxic effect of NSAIDs on the gastrointestinal tract, could be the combination of different antiplatelet effects of SSRIs and NSAIDs, with SSRIs reducing platelet serotonin levels and NSAIDs reducing thromboxane synthesis by inhibiting cyclooxygenase 1. The results of our study and that of Kurdyak et al[14] indicate that such synergism does not exist for concurrent use of coumarins and SSRIs; the effect of SSRIs on preexisting lesions in the gastrointestinal tract adds nothing to and is offset by the pharmacologically stronger anticoagulant effect of coumarins. However, the mechanism by which NSAIDs increase the risk of nongastrointestinal bleeding is no longer the potential damaging effect on the gastric mucosa but only the antiplatelet effect. Insofar as nongastrointestinal bleeding in our study is concerned, inhibition of platelet aggregation contributes to an increased risk of major bleeding in users of coumarins, making our similar point estimates for the ORs of SSRIs and NSAIDs plausible. More studies are needed to assess for which bleeding the risk is increased by concurrent use of SSRIs and coumarins. The second most frequently occurring and also most disabling category of bleeding is intracranial bleeding, for which results of the stratified analysis suggested a similar increased risk with NSAIDs and SSRIs, although statistical significance was not achieved for SSRIs, but NSAIDs showed a strong trend. This is probably a power effect. Power for finding a significantly increased OR of 1.6 in our study is only 24% for SSRIs and 44% for NSAIDs.

Our results suggest no indication for increased risk of either gastrointestinal bleeding or nongastrointestinal bleeding with nortriptyline and mirtazapine therapy, although the numbers were too small for reliable analysis. Because of the pharmacodynamic nature of the effect of SSRIs on bleeding risk in users of coumarins in our study, we believe our results also apply to warfarin sodium.

The percentages of the most frequently occurring bleeding events in our study are comparable to those found in a recently conducted pooled analysis of major bleeding in 7239 patients from 2 clinical trials in users of warfarin and ximelagatran.[23] In warfarin users, 34% of bleeding events were gastrointestinal and 18% were intracranial (and intracerebral) compared with 32.9% and 17.2% in our study.

Some limitations of our study must be considered. First, there is the possibility of misclassification of users of coumarins because we had to make assumptions about the duration of coumarin use. However, a reduction in the maximum time between the last dispensing date of a coumarin and the index date did not result in different outcomes, which suggests that our assumptions were valid. Second, we did not have data on the intensity of anticoagulation (normal or high) or on liver and renal insufficiency, which are also risk factors for major bleeding.[16,18] Third, because we could only evaluate a history of hospitalization for major bleeding from the time patients were included in the PHARMO Record Linkage System, we could have missed information about earlier bleeding in patients. Because we did not have information about bleeding not resulting in hospitalization, it is possible that our nonhospitalized–matched control subjects might have included some who had such bleeding previously. As a consequence, our conclusions apply to patients who were hospitalized because of bleeding vs patients who were not but in whom previous bleeding not resulting in hospitalization could have been present. Because of these limitations, additional prospective studies in coumarin users are needed to confirm our results and to assess which specific nongastrointestinal bleeding is most affected by SSRIs.

The results of our study indicate that the advantages of SSRIs in users of coumarins must be carefully weighed against the adverse effect of an increased bleeding risk. Given the limitations of our study, we cannot advise against concurrent use of SSRIs and coumarin anticoagulants; however, intensified monitoring of users of SSRIs seems justified. It is also possible to consider an alternative to an SSRI when initiation of antidepressant therapy is necessary in a patient using a coumarin. In conclusion, the results of our study strongly suggest that SSRI use is associated with an increased risk of hospitalization because of nongastrointestinal bleeding but not because of gastrointestinal bleeding.

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