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The influence of cyclo-oxygenase specificity of non-steroidal anti-inflammatory drugs on bleeding complications in concomitant coumarine users

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Summary

Background: Concomitant use of coumarines and non-steroidal anti-inflammatory drugs (NSAIDs) may induce bleeding complications, due to the inhibition of both coagulant factors and platelet function. Unlike non-selective NSAIDs, cyclo-oxygenase-2 (COX-2)-selective NSAIDs interfere very little with platelet aggregation.
Aim: To determine whether COX-2-selective NSAIDs are associated with less bleeding complications in coumarine users, compared with non-selective NSAIDs.
Design: Prospective, nested case-control study.
Methods: We studied concomitant coumarine and NSAID users over two years. Patients with bleeding (cases), and frequency-matched patients without bleeding (controls), were sent questionnaires regarding possible risk factors for bleeding. International normalized ratio (INR) values were recorded. Univariate and multivariate analyses were used to detect factors contributing to bleeding.
Results: There were 1491 reported bleeds. NSAIDs were involved in 14.8%; 3.9% involving COX-2-selective NSAIDs. In non-bleeders, 2601 prescriptions with a coumarine/NSAID combination were detected; 9.7% were COX-2-selective. Adjusted ORs (95% CI) for a bleeding complication were 3.07 (1.18–8.03) for non-selective NSAID use, 3.01 (1.42–6.37) for NSAID use >1 month, and 1.89 (1.03–3.49) for INR $\geq$ 4.0.
Discussion: In coumarine users, COX-2-selective NSAIDs are associated with less bleeding complications than non-selective NSAIDs are. Duration of NSAID use, as well as intensity of coumarine treatment, plays an important additional role. When the coumarine-NSAID combination is inevitable in an individual patient, a COX-2-selective NSAID may be preferred, with careful monitoring of the INR.

Introduction

Bleeding is a well-known complication of aspirin and of other non-steroidal anti-inflammatory drugs (NSAIDs). The occurrence of bleeding during the use of NSAIDs is predominantly explained by their effect on platelet function. The NSAID inhibition of the cyclo-oxygenase-1 (COX-1) enzyme in platelets interferes with thromboxane synthesis, leading to inhibition of platelet aggregation.[1] The association of upper gastrointestinal haemorrhages with the use of NSAIDs is well known;[2–7] NSAID-related bleeding at other locations has been investigated less thoroughly.[8,9]

Recently, COX-2-selective NSAIDs (the so-called COXIBs: rofecoxib, celecoxib) have been introduced. These NSAIDs block COX-2, leading to decreased prostaglandin synthesis and thus to less inflammation, comparable with the non-selective NSAIDs. However, the COX-2-selective NSAIDs

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(relatively) spare the COX-1 enzyme in gastrointestinal mucosa as well as in platelets.[10,11] Consequently, compared to the non-selective NSAIDs, the COX-2-selective NSAIDs cause less gastrointestinal damage[12,13] and show less interference with platelet function in *in vitro* studies.[14,15] Similarly, the NSAIDs meloxicam and nabumetone interact little or not at all with gastrointestinal and platelet function. These may therefore considered to be at least partially COX-2-selective.[16–18]

The question as to whether bleeding complications occur less with COX-2-selective NSAIDs, compared with non-selective NSAIDs, is clinically relevant, especially in high-risk populations such as the users of coumarine derivatives: a previous survey of 25 studies showed the bleeding rate in coumarine users to be 9.6 % per year,[19] identifying the duration of coumarine use and the degree of anticoagulation (as indicated by the International Normalized Ratio, INR) as the most important factors associated with bleeding. Until now, the risk of bleeding due to concomitant NSAID and coumarine use has been little investigated. There are some studies on the influence of NSAID use on the INR,[20–24] and one study on the effect on gastrointestinal bleeding.[25] Recently, we have shown that NSAIDs substantially raise the bleeding incidence of coumarine users in Enschede, the Netherlands.[26]

The primary goal of this study was to investigate the influence of COX-2-selective vs. non-selective NSAIDs on bleeding complications in coumarine users.

Methods

The study was performed over two years (September 1998 to September 2000) in the well-defined geographical area of the city of Enschede, the Netherlands. This region, with about 160 000 inhabitants, borders on Germany. In-patient health care is provided by only one teaching hospital, supplied with all diagnostic and therapeutic equipment; referral to other hospitals hardly ever occurs. Medication is supplied by the 15 pharmacies in the city, all using standardized and computerized pharmacy databases. Ambulant coumarine users are cared for by the only anticoagulation office in the city, which records and regulates the degree of anticoagulation (as indicated by the INR). Long-term anticoagulation (> 6 months) is given to 78 % of patients. Approximately two-thirds of them receive high-intensity anticoagulation, aiming for an INR between 3.0 and 4.0. The INR of all short-term patients and of the rest of the long-term patients is aimed at between 2.5 and 3.5. For a small minority, the target INR is between 2.0 and 3.0. All coumarine users have been instructed at therapy start to report every bleeding complication to the anticoagulation service. Prior to the start of the study, they were reminded of this in a standardized manner.

The study was performed in the Enschede cohort of combined coumarine and NSAID users. These could be identified using the databases of the 15 collaborating pharmacists, with registration of age and gender of the patient, as well as the type of both the NSAID and the coumarine used. Bleeding complications were defined as visible blood loss (regardless of the amount) from any location, haematoma not explained by a clear trauma, black tar stools (without iron supplementation) and intracerebral haematoma as seen on computer tomography and/or magnetic resonance imaging.

A nested case-control design was applied. *Cases* were defined as patients who experienced a bleeding complication during concomitant coumarine and NSAID therapy. NSAID users were defined as patients who used an NSAID dose at least once in the preceding month. Databases of both the anticoagulation office and the hospital were used for the identification of patients with bleeding. The diagnosis registration system of the hospital was complementary, and detected especially the serious, possibly lethal bleeding and bleeding during admission otherwise not spontaneously reported to the anticoagulation office. The month of the bleed was set as the target month. *Controls* were defined as patients not experiencing a bleeding complication while using a coumarine/NSAID combination. To select them, frequency matching with the cases was applied for age and gender. The controls were selected from the same target month as the cases.

Cases and controls were all sent a questionnaire, with the possibility to return it anonymously and free of charge; both the individuals who did this and the admitted patients for whom hospital data were available were marked as responders. The questionnaire was similar for cases and controls, with the target month clearly indicated on the first page. It contained 13 items. Some general issues were addressed in the first three items (age, gender, type and indication of coumarine). Then, in the next three items, medication use was recorded, especially the dose and duration of NSAIDs. The next four items in the questionnaire were dedicated to the location and consequences of the bleeding. Finally, additional risk factors for bleeding complications were addressed in the last three items: specifically, comorbidity, smoking, and alcohol use were recorded. Where answers were incomplete or unclear, patients were contacted by telephone.

Three INR values were recorded from all responders (cases and controls): target INR, most recent INR and mean INR in the previous month. For the latter two INR values, an index date was set: the date of the bleeding for the bleeders and the day closest to the 15th of the target month for the non-bleeders.

All patients gave informed consent. The local Ethics Committee approved the study.

Statistics

To compare the different groups, t-tests (independent samples) were used for continuous variables and χ^2 tests for dichotomous variables. To determine the influence of various factors on the occurrence of bleeding, univariate tests (χ^2 tests with assessment of odds ratio) were performed, using the SPSS 10.0 program. The same statistical program was applied for multivariate, logistic regression analysis, incorporating both categorical and continuous variables. Results are given as means (SD), and 95% CIs are presented where appropriate.

Results

During the two years of the study, 1491 bleeding incidents were reported in the population of coumarine users. The mean age of the patients was 71 years, and more men than women were involved (56% vs. 44%). Gastrointestinal bleeding occurred 118 times, intracerebral bleeding 31 times. In 15 cases, the bleeding was lethal, but in general, the bleeds were minor (Table 1). We received 976 returned questionnaires, and the hospital diagnosis registration system accounted for additional data on 73 bleeds, leading to reliable data on 70% of all bleeds. These are further indicated as 'responders' ($n=1040$), who did not differ significantly from non-responders with regard to age, gender, coumarine type, and indication for coumarine use (data not shown). The site of the bleeding was also comparable in both groups (Table 1).

In 14.8% of the bleedings, an NSAID had been used in the preceding month ($n=154$; *cases*). Location of bleeding was comparable among the NSAID and non-NSAID users. Lethal bleedings did not occur more often in the NSAID users (Table 1). The six bleedings in COX-2-selective NSAID users occurred in the nose ($n=3$), gastrointestinal tract ($n=1$), skin ($n=1$), and conjunctiva ($n=1$).

Among the 2601 non-bleeders with concomitant coumarine/NSAID use, 589 frequency-matched controls were selected, of whom 183 returned the questionnaire (31%). No differences were found between responding and non-responding controls with regard to age, gender, and type of coumarine (data not shown). In addition, no significant differences were found between cases and controls (Table 2). The controls used more COX-2-selective NSAIDs than the cases did (12.0% vs. 3.9%) (Table 3). Among NSAID users (with or without bleeding), the INR did not significantly differ between COX-2-selective NSAIDs and non-selective NSAIDs (most recent INR: mean (SD) 3.20 (0.77) vs. 3.43 (1.32), and INR in previous three months: 3.09 (0.44) vs. 3.26 (0.61)). In addition, the age of the COX-2-selective NSAID users was comparable with that of the non-selective NSAID users (70.4 (10.1) vs. 71.0 (9.7) years). However, COX-2-selective NSAID users were on coumarine therapy for a longer period (70.8 (52.6) vs. 59.8 (65.9) months). Moreover, COX-2-selective NSAID users had their NSAID for a shorter period than the non-selective NSAID users (8.3 (9.8) vs. 32.5 (44.9) months). In addition, they used higher daily doses of their NSAID (data not shown).

In the univariate analyses, five factors were related to the occurrence of a bleeding compli-

Table 1 Bleeding complications in all coumarine users (n=1491), and in responders (n=1040; with versus without concomitant NSAID use)

		Responders	
	All	With NSAID use (*cases*, $n=154$)	Without NSAID use ($n=886$)
Skin	35.1	35.1	30.5
Nose	24.5	24.7	27.0
Conjunctiva	15.6	11.7	15.9
Urine	9.0	9.7	8.0
Gastrointestinal	7.9	11.7	8.7
Intracerebral	2.1	1.3	2.9
Muscle	1.1	1.2	1.7
Respiratory	1.1	–	1.0
Postoperative	0.9	2.6	1.1
Genital	0.8	–	1.1
Joint	0.5	–	1.0
Miscellaneous	1.5	1.8	1.1
Lethal	NA	0.6*	1.6**

All data are given in percentages. NSAIDs, non-steroidal anti-inflammatory drugs. Miscellaneous: sites of bleeding with frequency <1.0 % in the whole responder group. NA, not applicable. *Lethal bleeding with NSAID: in tumour ($n=1$). **Lethal bleeding without NSAID:intracerebral ($n=12$), respiratory ($n=1$), and aortic aneurysm ($n=1$). No significant differences regarding bleeding site were found between the two groups (with or without concomitant NSAID use).

Table 2 General characteristics of cases and controls

	Cases ($n=154$)	Controls ($n=183$)
Mean (SD) age (years)	71.1 (10.8)	72.0 (7.7)
Men:women (%)	53.9 : 46.1	56.8 : 43.2
PP:AC (%)	59.1 : 40.9	53.0 : 47.0
Indication for coumarine (%)		
Arrhythmia	26.0	23.5
Peripheral arterial disease	22.7	25.7
Coronary disease	18.8	20.2
Venous thrombosis	13.0	4.9
Joint prosthesis	7.8	8.2
Valvular disease	7.1	7.1
Cerebrovascular disease	4.5	10.2
Miscellaneous	0.0	0.0

NSAIDs, non-steroidal anti-inflammatory drugs. Cases, concomitant coumarine/NSAID use and bleeding; controls, concomitant coumarine/NSAID use with no bleeding. PP, phenprocoumon; AC, acenocoumarol; no patient used warfarin.

Table 3 Type of NSAIDs in cases and controls

	Cases ($n=154$)	Controls ($n=183$)
COX-2-selective NSAIDs	3.9	12.0
Nabumetone	2.6	4.4
Meloxicam	1.3	3.8
Rofecoxib	0.0	3.8
Celecoxib*	0.0	0.0
Non-selective NSAIDs	96.1	88.0
Diclofenac, without misoprostol	50.0	42.6
Diclofenac, with misoprostol	2.6	10.4
Ibuprofen	21.4	26.2
Naproxen	7.1	2.7
Indomethacine	5.2	1.1
Ketoprofen	4.5	1.6
Piroxicam	3.9	2.7
Tiaprofenic acid	0.6	0.5
Flurbiprofen	0.6	0.0
Phenylbutazone	0.0	0.0
Aceclofenac	0.0	0.0
Sulindac	0.0	0.0
Prolixan	0.0	0.0

All data are given in percentages. NSAIDs, non-steroidal anti-inflammatory drugs. Cases, concomitant coumarine/NSAID use, bleeding; controls, concomitant coumarine/NSAID use, no bleeding. COX, cyclo-oxygenase. *During the study, celecoxib was not yet on the Dutch market.

cation: the use of a non-selective NSAID, longer duration of NSAID use, shorter duration of coumarine use, stronger anticoagulation (as indicated by a higher INR), and absence of a previous cerebrovascular accident (CVA). NSAID dose, age, gender, other co-medication and/or co-morbidity, smoking, and alcohol use were not important risk factors (Table 4). Multivariate regression analysis, with the occurrence of bleeding as dependent variable, identified four factors with a substantially increased odds ratio: non-selective NSAID use (as compared to COX-2-selective NSAID), longer NSAID use, higher INR, and absence of CVA (Table 5).

Discussion

The present study of concomitant coumarine and NSAID users shows that COX-2-selective NSAIDs are associated with a decreased risk of bleeding complications compared to non-selective NSAIDs.

A randomized, double-blind, placebo-controlled study would have been the ideal model to address our primary question. However, such a design would require the deliberate prescription of NSAIDs to coumarine users, in spite of their theoretical bleeding risk. We consider this to be unethical. Taking this into consideration, a nested case-control design seems to be most appropriate to address our question. Such a design needs a well-described area in which all patients are cared for by the same health institutions in order to collect all cases (concomitant coumarine and NSAID users with a bleeding complication). This is definitely the case in the Enschede region, where 15 co-operating pharmacists, who all have standardized, computerized databases, deliver all prescribed medication. Moreover, only one anticoagulation office treats all coumarine users. At most, a single bleeding occurring outside the described region may have been missed, assuming that the involved patient also ignored the strong advice to report every bleeding to the anticoagulation service.

The response rate on the questionnaires in our study differed between cases and controls. Two reasons may explain this. First, patients without a bleeding complication may be less motivated to participate in a study on bleeding complications. Second, due to the matching procedure, controls received the questionnaire somewhat later than the cases but had to complete it on the same target month as the cases. Possibly, some controls had difficulties in describing their situation of some months earlier. However, we did not find indications for selection bias for either cases or controls, since responders and non-responders were

Table 4 Comparison (univariate analysis) of cases and controls with regard to various possible risk factors for bleeding complications during concomitant coumarine and NSAID use

	Cases	Controls	Odds ratio	95% CI
Anticoagulation				
Mean INR (previous 3 months) > 4.0	13	5	2.92	1.28–6.67
Most recent INR > 4.0	27	14	2.22	1.29–3.84
Coumarine use ≥ 6 months	21	15	1.51	0.85–2.70
Phenprocoumon (vs. acenocoumarol)	59	53	1.28	0.83–1.98
NSAID use				
Non-selective (vs. COX-2-selective) NSAID	96	88	3.33	1.33–8.33
NSAID use > 1 month	91	81	2.35	1.19–4.65
Daily dose above maximum dose	7	3	2.56	0.86–7.76
Daily dose above DDD	28	26	1.07	0.66–1.73
Patient characteristics				
Prednisolone use	11	6	1.85	0.83–4.13
Age > 65 years	22	14	1.72	0.98–3.03
Previous gastrointestinal incident	15	11	1.40	0.73–2.70
Smoking	28	23	1.32	0.80–2.18
Diabetes mellitus	15	16	0.91	0.50–1.68
Male sex (vs. female)	54	57	0.88	0.58–1.37
Alcohol consumption	41	45	0.87	0.56–1.35
Acetaminophen use	35	44	0.67	0.43–1.05
Atrial fibrillation	30	39	0.66	0.42–1.06
Acetylsalicylic acid use	0.6	1.1	0.59	0.05–6.59
Previous cerebrovascular incident	11	19	0.53	0.28–1.01
SSRI use	2	7	0.30	0.08–1.07

All data are given in percentages. NSAIDs, non-steroidal anti-inflammatory drugs. Cases, concomitant coumarine/NSAID use, bleeding; controls, concomitant coumarine/NSAID use, no bleeding. INR, international normalized ratio. Maximum dose: NSAID dose above which toxic effects may be expected, as indicated (for the Dutch situation) by the *Farmacotherapeutisch Kompas*.[40] DDD, Daily Defined Dose—mean dose for an adult person, needed for treatment of the main indication of the medicine (assessed by the WHO Collaborating Centre for Drug Statistics Methodology[40]). SSRI, selective serotonin reuptake inhibitor.

Table 5 Multiple regression analysis (incorporating significant factors found in the univariate analysis) for the occurrence of bleeding with concomitant coumarine and NSAID use

Factor	Reference	Adjusted OR	95% CI	*p*
Non-selective NSAID	COX-2-selective NSAID	3.07	1.18–8.03	0.022
NSAID use > 1 month	NSAID use ≤ 1 month	3.01	1.42–6.37	0.004
Mean INR > 4.0	Mean INR ≤ 4.0	2.27	0.92–5.58	0.074
Last INR > 4.0	Last INR ≤ 4.0	1.89	1.03–3.49	0.041
Duration of coumarine use (months)	NA	1.00	1.00–1.01	0.228
Previous CVA	No previous CVA	0.38	0.19–0.76	0.006

NSAIDs, non-steroidal anti-inflammatory drugs. COX-2, cyclo-oxygenase-2; INR, international normalized ratio; CVA, cerebrovascular accident. NA, not applicable (continuous factor).

comparable for several important factors (age, gender, type of coumarine and of NSAID, bleeding location). Recall bias seemed to have played a minor role as well, since patients were contacted by phone whenever data on the questionnaire were unclear, incomplete or inconsistent with the data from either their pharmacist or the anticoagulation service.

Using univariate analysis, a lower incidence of cerebrovascular disease in the cases (as compared with the controls) was found. In the absence of a plausible explanation, this may have been sheer coincidence; moreover, this factor did not turn out to be important in the multivariate analysis.

A previous overview of coumarine-related bleedings identified the same risk factors as in the present

study:[19] early phase of coumarine therapy and high INR. Most of the coumarine-related bleedings in our study could be considered minor, being located primarily in the skin, the nose and the conjunctiva. Although these bleedings seldom require extensive medical treatment, they do mean a substantial burden for the patient. Therefore, we consider it important to include them in the analyses.

Previous studies on bleeding due to NSAIDs (without concomitant coumarine use) mainly focussed on the gastrointestinal tract. Several case control studies in patients with upper gastrointestinal bleeding showed high ORs for the use of NSAIDs[2–7] even without including aspirin. Most of these studies were performed before the introduction of COX-2-selective NSAIDs. In one study, an association was found with duration and dose of the used NSAID, in accordance with the present study. Few data are available on other bleedings due to NSAIDs. In a case-control study in patients with haematuria, a high OR for previous NSAID use was demonstrated.[8] Another case-control study on cerebrovascular haemorrhage did not find an association with NSAID use.[9] In contrast, the present study shows that, with NSAID use, the frequency of bleeding increases at all locations, underscoring the importance of COX inhibition in platelets.

So far, knowledge on bleeding associated with the combination of coumarines and NSAIDs has been scarce. Some case reports have been published in which bleeding occurred in coumarine users after the introduction of an NSAID (indomethacine, nabumetone and celecoxib).[27–31] One case-control study in elderly patients with upper gastrointestinal bleeding showed higher ORs for coumarine and NSAID monotherapy compared to no medication (3.3 and 4.0, respectively); in the same study, a higher OR was demonstrated for the combined use of coumarines and NSAIDs as compared to coumarine use alone (3.0).[25] Although in that study COX-2-selective NSAIDs were not included, the results accord with the present findings.

Other prospective studies did not focus on the incidence of bleeding, but rather on the effects of NSAIDs on the INR, after adding them to coumarine therapy. Both coumarines and NSAIDs are highly protein-bound. Thus NSAIDs may displace coumarines from their protein binding sites, leading to higher coumarine concentrations and consequently higher INRs. Indeed, warfarin was shown to be displaced from its protein binding sites by phenylbutazone, fenbufen, isoxicam, and naproxen;[32–35] however, in most cases, there was no increase in INR. Warfarin is seldom prescribed in the Netherlands, and until now, only a few studies focussed on the interaction between the two other coumarine derivatives and NSAIDs. When flurbiprofen and naproxen are concomitantly prescribed with phenprocoumon, INR is increased.[20–22] However, diclofenac, nabumetone, and tiaprofenic acid interfered with neither phenprocoumon nor acenocoumarol.[23,24] In the present study only these two coumarine types were used. In addition, INRs were comparable for the COX-2-selective and the non-selective NSAID users. Thus, the direct interaction between NSAIDs and coumarines seems to be less important than the COX-2-selectivity of the NSAIDs for the occurrence of bleeding.

Our results support earlier findings that COX-2-selective NSAIDs do not interfere with platelet function, while non-selective NSAIDs do.[14,15,36] Although COX-2 selectivity is less documented for nabumetone and meloxicam than for rofecoxib and celecoxib, in *in vitro* studies, platelet function is only slightly inhibited by either nabumetone or meloxicam.[17,18,37–39] Since interference with platelet function is the main factor by which NSAIDs can increase the bleeding risk in coumarine users, these two NSAIDs were grouped together with rofecoxib as COX-2-selective NSAIDs in the present study. Celecoxib had not been introduced on the Dutch market, and rofecoxib became available only in the last 5 months during the study. Thus, nabumetone and meloxicam largely accounted for the favourable results of the COX-2-selective NSAIDs. Repeating the study nowadays (with substantial use of the more COX-2-selective rofecoxib and celecoxib), might show even more pronounced differences between the two NSAID classes.

In conclusion, when NSAIDs and coumarines have to be combined, the preferred choice may be a COX-2-selective NSAID. The concomitant use of NSAIDs and coumarine should be as short as possible. Although NSAID therapy does not raise the INR relevantly, higher INR seems to be an independent risk factor for bleeding complications and needs to be avoided.

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