Drug interactions as a cause of overanticoagulation on phenprocoumon or acenocoumarol predominantly concern antibacterial drugs

Background: The risk of hemorrhage when coumarin anticoagulants are used sharply increases when the international normalized ratio (INR) is ≥6.0. Such overanticoagulation may be caused by drug interactions. We performed a case-control study among previously stable outpatients of an anticoagulation clinic using phenprocoumon or acenocoumarol to identify changes in the use of potentially interacting drugs related to overanticoagulation.

Methods: Three hundred case patients with INR values ≥6.0 were compared with 302 randomly selected matched control subjects with INR values within the target zone. Information on changes in the use of 87 potentially interacting drugs in the 4 weeks before the index day was collected by interviewing patients and by reviewing the anticoagulant medical record.

Results: Forty-five potentially interacting drugs were not used in the 4-week study period, and only 15 drugs were used by at least 10 patients. For a number of drugs, too few patients had a relevant change in use to judge their association with overanticoagulation. A course of a combination product of sulfamethoxazole and trimethoprim strongly increased the risk of overanticoagulation (adjusted odds ratio, 24.2; 95% confidence interval [CI], 2.8 to 209.1; population attributable risk percentage [PAR%], 5.7%), especially in patients receiving acenocoumarol. Penicillins were associated with a risk of overanticoagulation of 2.4 (95% CI, 1.00 to 5.5); the corresponding PAR% was 3.4%. The effect was confined to amoxicillin (INN, amoxicilline) plus clavulanic acid.

Conclusion: Drug interactions as a cause of overanticoagulation predominantly concerned antibacterial drugs. If possible, the use of sulfamethoxazole-trimethoprim and amoxicillin plus clavulanic acid should be avoided in patients receiving coumarins. If there is no therapeutic alternative available, increased monitoring of INR values is warranted to prevent overanticoagulation and potential bleeding complications. (Clin Pharmacol Ther 2001;69:451-7.)

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Coumarin anticoagulants are widely used in the prevention of venous and arterial thromboembolism [1] These drugs induce anticoagulation by antagonizing vitamin K and thereby impairing the biological activity of the vitamin K–dependent coagulation factors (factor II, VII, IX, and X) [2] Opposite their benefit stands the risk of hemorrhage,[3] which is strongly associated with the intensity of anticoagulation and sharply increases when the international normalized ratio (INR) is ≥6 0 [4 5] Such overanticoagulation may be caused by drug-drug interactions, and coumarin anticoagulants are extremely susceptible to drug-drug interactions because of their narrow therapeutic range [6] Critical periods are when a patient stabilized on an anti-

coagulant regimen starts treatment with an interacting drug or when a patient stabilized on a regimen of an interacting drug and an anticoagulant has the interacting drug withdrawn.[7] A considerable number of drug interactions with coumarin anticoagulants, based on case reports and small-scale experiments, have been reported and summarized.[6-9] However, epidemiologic studies that quantify the role of drug interactions in overanticoagulation in a nonselected population on coumarins under everyday circumstances are scarce. Therefore we conducted a prospective nested case-control study among outpatients of an anticoagulation clinic. We identified changes in the use of potentially interacting drugs related to an INR ≥6.0 in previously stable patients who were taking phenprocoumon or acenocoumarol, and we calculated the corresponding odds ratios (OR) and population attributable risk percentages (PAR%). This article is one of a series of 3 papers on risk factors for overanticoagulation. The other 2 articles are based on the same study and concern characteristics of anticoagulant therapy and comorbidity and sociodemographic, lifestyle, and dietary factors.

METHODS

Setting. In the Netherlands, anticoagulant therapy is monitored by a network of more than 60 independently operating specialized anticoagulation clinics that cover more than 90% of the country.[10,11] The study was performed at the regional Red Cross Anticoagulation Clinic, The Hague, which serves an area of nearly 700,000 inhabitants. All persons in this area with an indication for anticoagulant therapy are referred to this clinic.

Cohort definition. The study cohort consisted of all patients treated with oral anticoagulants by the regional Red Cross Anticoagulation Clinic, The Hague, between December 1, 1997, and June 14, 1999. All cohort members were monitored until the first occurrence of an INR ≥6.0, the end of their treatment, or the end of the study period (ie, the day on which the planned number of case patients was recruited), whichever came first.

Case patients and control subjects. Subjects for the nested case-control study were identified daily from all patients with an INR measurement on that day. Case patients were defined as cohort members with INR values ≥6.0. For each case patient, 1 control subject, matched on therapeutic range, was randomly selected from the cohort members with INR values within the target zone (2.0 to 3.5 or 2.5 to 4.0), measured on the same day as the case patient (index day). Overanticoagulation is often seen during initiation of anticoagulant therapy and in unstable anticoagulation. Because this was not our primary interest, only case patients and control subjects with stable anticoagulation in the 3 months before the index day were eligible. Anticoagulant therapy is considered to be effective and safe if the patient is kept within the target zone for more than two-thirds of the time.[12,13] We therefore defined stable anticoagulation as having at least 66% of the INR values within the target zone and no INR values ≥5.5 in the 3 months before the index day. To judge stability, a minimum of 3 INR values had to be assessed in the 3 months before the index day. Case patients and control subjects with a hospital admission in this period were excluded because information on anticoagulant control during admission is often not available at the anticoagulation clinic. We focused on sudden overanticoagulation, therefore the INR preceding the assessment on the index day had to be within the target zone. Because of questions about medication and diet, the patients had to be living independently and not making use of Meals on Wheels. We were primarily interested in overanticoagulation, regardless of whether it was followed by hemorrhage, therefore patients who came to the clinic on the index day with a serious bleeding complication were excluded because it might have promoted recall bias.

Procedure. The study protocol was approved by the Medical Ethics Committee of the Erasmus University Medical Center Rotterdam. We planned to recruit 300 case patients and 300 control subjects to provide at least an 80% power to detect a true OR of ≥2.0 for risk factors that had a prevalence of 7% among the control subjects, with $P < .05$ used to reject the null hypothesis of OR = 1.

Information on changes in drug use, potential confounding factors, and effect modifiers was collected from the anticoagulant medical record, through the general practitioner and the pharmacy, as well as by interviewing the patient. The interview took place within 3 weeks after the index day at the private address of the patient, making use of structured questionnaires with mainly closed questions. The interviewers were blinded with respect to each patient's case or control status and the specific research hypotheses. This also applied to the general practitioners and the pharmacists. Blinding of the patients was not fully feasible because the INR value was printed on their dosage list. To obviate this, in the information letter we referred to the problem of overanticoagulation in a general sense.

Changes in drug use. The risk period was defined as the 4-week period before the index day. Patients were asked to show all currently taken prescription and over-

the-counter drugs and vitamin supplements. The dosage and frequency of use of these drugs and vitamins were recorded. Patients were asked about dosage changes in the risk period, drugs and vitamins that were started in the risk period, and drugs and vitamins that were discontinued in the risk period. Information in the anticoagulant medical record on dosage changes, start, or discontinuation of a drug was also considered. Of all patients, the medication history of the preceding 6 months was obtained from the pharmacy. This history was used to judge the reliability of the patient interview data and anticoagulant medical record data on changes in drug use.

On the basis of overviews of drugs interacting with anticoagulant therapy,[6-8] 69 drugs and 18 drug classes were a priori considered to be potentially interacting drugs. Because changes in drug use, rather than continuous drug use, pose a risk of overanticoagulation,[7] the occurrence of the following situations was defined for every patient by use of patient interview data and anticoagulant medical record data: start, dose increase, or irregular and infrequent use (ie, 1 or 2 times a week) of a potentially interacting drug or vitamin that enhances the anticoagulant effect, as well as discontinuation, dose reduction, or irregular and infrequent use of a potentially interacting drug or vitamin that diminishes the anticoagulant effect.

Cofactors. A change in drug use, especially a course of antibacterial drugs and the use of analgesics, most probably occurs in case of an acute illness or a relapse of a chronic comorbidity. These situations may be accompanied by fever or may result in a change in weight, physical activity, dietary intake (and thereby intake of vitamin K), or alcohol consumption. All of these factors may affect the response to oral anticoagulants[2,9,14-18] and were therefore considered to be potential confounders. The associations between these cofactors and overanticoagulation are the main subjects of the 2 other articles mentioned earlier.

Furthermore, effect modification by the type of anticoagulant may be present. Drugs may interact with coumarin anticoagulants by inducing or inhibiting specific cytochrome P450 enzymes, especially cytochrome P450 2C9 (CYP2C9).[6,8,19] The difference in the structure of acenocoumarol and phenprocoumon, although small, may have implications on the relative contribution of cytochrome P450 enzymes to their metabolism.[20] The risk of overanticoagulation when the use of CYP2C9-mediated drugs changes therefore possibly differs with the type of anticoagulant used.

Statistical analyses. Changes in the use of potentially interacting drugs (vitamin supplements included) related to an INR value ≥6.0 were identified with use of univariate conditional logistic regression analysis at first. Because the unconditional analyses gave comparable results but more statistical power, we finally used unconditional logistic regression analysis to compute unadjusted OR values and their 95% CI values. In case a risk factor was absent in either the case patients or the control subjects, a Fisher exact test was performed instead. To assess changes in drug use that were independently associated with an INR value ≥6.0, all factors that were univariately associated at $P < .10$ were included in a multiple regression model. Besides age, sex, and the number of INR determinations in the preceding 3 months, cofactors that were univariately associated with an INR value ≥6.0 were included if this resulted in a change in one of the odds ratios of 5% or more, starting with the most potent factor. Effect modification by the type of anticoagulant was studied by performing stratified analyses.

To determine the importance of the independent risk factors for overanticoagulation in the population, we calculated the population attributable risk percentages (PAR%) according to the following formula[21]:

$$\text{PAR\%} = \text{AR\%} \cdot (\text{proportion of exposed case patients})$$
$$\text{with AR\%} = ([\text{OR} - 1]/\text{OR}) \cdot 100$$

RESULTS

The nested case-control study included the planned number of 300 case patients with a median INR of 6.8 and 302 control subjects with a median INR of 3.2. The participation among case patients and control subjects was 78% and 85%, respectively. Written informed consent was obtained from every patient. The mean interval between the index day and the interview was 14 days for case patients and for control subjects. Characteristics of the study population are presented in Table I. Fifty-five percent of the case patients and 66% of the control subjects used phenprocoumon, and the others used acenocoumarol. The mean number of prescription and over-the-counter drugs regularly and frequently used, besides the anticoagulant, and the number of patients using health supplements was similar for case patients and control subjects.

Of 87 potentially interacting drugs or drug classes, 45 were not used by the study population in the 4-week risk period and 27 were used by fewer than 10 patients. The drugs and drug classes used by at least 10 patients are listed in Table II; about one-third of the patients had used acetaminophen (INN, paracetamol) in the risk period and one-fourth had used 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors; the remain-

Table I. Characteristics of the study population*

Variable	*Case patients (n = 300)*	*Control subjects (n = 302)*	*OR [95%CI]*
Age, mean ± SD (y)	68.1 ± 12.3	68 2 ± 9.8	1.00 [0.98-1.01]
Sex			
Male	175 (58%)	194 (64%)	1 [reference]
Female	125 (42%)	108 (36%)	1.3 [0.9-1 8]
Indication for anticoagulation			*P* = .51
Atrial fibrillation	37	40	
Prosthetic heart valve	31	31	
Heart disease	110	131	
Peripheral arterial disease	76	66	
Cerebrovascular thromboembolism	28	18	
Venous embolism	16	13	
Prophylactic treatment	2	3	
Type of anticoagulant			
Phenprocoumon	165 (55%)	200 (66%)	1 [reference]
Acenocoumarol	135 (45%)	102 (34%)	1.6 [1.2-2.2]
No. of drugs, mean ± SD†	3.5 ± 2.7	3.7 ± 2.6	1.0 [0.9-1.04]
Use of health supplements			
Any supplement	95	111	1.3 [0.9-1.8]
Vitamin C	21	18	1.2 [0.6-2.3]
Vitamin D	6	6	1.0 [0.3-3.2]
Vitamin E	6	6	1.0 [0.3-3.2]
Multivitamins	39	33	1.2 [0.7-2.0]

OR, Odds ratio, CI, confidence interval
*Values are numbers unless indicated otherwise
†Prescribed and over-the-counter drugs regularly and frequently used (ie, at least 3 times a week) besides the anticoagulant

ing drugs were used by fewer than 46 patients. A relevant change in use in the risk period occurred in at least 10 patients each only for acetaminophen, doxycycline, amoxicillin (INN, amoxicilline), amoxicillin plus clavulanic acid, and sulfamethoxazole-trimethoprim. Comparison of the information on the start of antibacterial drugs given by the patient or mentioned in the anticoagulant medical record with that subtracted from the medication history revealed no substantial differences in either the case patients or the control subjects.

The associations between overanticoagulation and changes in drug use are shown in Table III. A course of antibacterial drugs was associated with an INR ≥6.0 (OR, 2.8; 95% CI, 1.8 to 4.5). In view of a difference in mechanism of interaction and to be more informative, all antibacterial drugs were also studied individually. Sulfamethoxazole-trimethoprim most strongly increased the risk of overanticoagulation. After adjustment for confounding factors, the increased risk was 24.2 (95% CI, 2.8 to 209.1). The corresponding PAR% was 5.7%. Penicillins were associated with an increased risk of an INR ≥6.0 of 2.4 (95% CI, 1.00 to 5.5). Adjustment for confounders did not change the OR. The PAR% of overanticoagulation associated with the use of penicillins was 3.4%. The effect of penicillins was confined to amoxicillin plus clavulanic acid. Doxycycline was only univariately associated with overanticoagulation (OR, 2.3; 95% CI, 1.1 to 4.6). Fluoroquinolones and clarithromycin were not related to an INR ≥6.0; however, the number of patients was small. The stratified analyses revealed that the effect of sulfamethoxazole-trimethoprim on the risk of overanticoagulation depended on the type of anticoagulant used and was especially present in patients taking acenocoumarol.

The analgesic used mainly was acetaminophen. Its use was associated with an increased risk of overanticoagulation of 1.5 (95% CI, 0.98 to 2.2). Adjustment for confounding factors reduced the OR to 1.2.

DISCUSSION

We studied the role of drug interactions in overanticoagulation among outpatients of an anticoagulation clinic. Half of the 87 potentially interacting drugs or drug classes were not used by the study population and only 15 drugs or drug classes were used by more than 10 patients. A relevant change in use in the risk period was infrequent. A course of sulfamethoxazole-trimethoprim and the use of amoxicillin plus clavulanic acid, however, were risk factors for overanticoagulation. The clinical implication of our findings is the possibility of

prevention or early detection of overanticoagulation, and thus of bleeding complications, by considering the use of antibacterial drugs other than sulfamethoxazole-trimethoprim and amoxicillin plus clavulanic acid. If there is no therapeutic alternative available, increased monitoring of INR values is warranted, that is, measuring the INR on the third day after the start of the antibacterial drug and, relative to this INR, 3 to 7 days thereafter. Our study also suggests that acetaminophen is a safe analgesic for patients receiving oral anticoagulants.

Many drugs postulated to interact with anticoagulant therapy on the basis of case reports and small-scale experiments were not used by our study population or by fewer than 10 patients. This is a reassuring observation, suggesting that these drugs did not play a major role in overanticoagulation in everyday circumstances. In addition, a change in drug use occurred infrequently for many of the 87 drugs. Although we could not judge their association with overanticoagulation because of the small numbers, this finding suggests that these drugs played only a minor role in our study population. Our results regarding the role of drugs in overanticoagulation likely may be generalized because the kinds of drugs used in our population is largely the same as those used in most other countries.

The types of coumarin used by our study population were phenprocoumon and acenocoumarol. In many countries warfarin is the coumarin of first choice. The results of our study, however, will largely apply to these countries as well. First, interactions of a pharmacodynamic nature on a receptor level occurring with one anticoagulant may well apply to another anticoagulant.[7] Second, the difference in half-life between coumarins will influence the time of onset and the duration of overanticoagulation[6] but will not necessarily affect the baseline risk. Third, drugs that interact by inducing or inhibiting the cytochrome P450 isozyme CYP2C9 will affect both acenocoumarol and warfarin.[20]

Two mechanisms have been suggested for antibiotic-associated hypoprothrombinemia.[22] First, antibacterial drugs affect the vitamin K status by eliminating vitamin K–producing microorganisms from the colon. Second, certain antibacterial drugs directly inhibit the synthesis of the vitamin K–dependent coagulation factors. High-risk antibiotics are cephalosporins that contain the *N*-methylthiotetrazole moiety. In patients receiving anticoagulant therapy, sulfamethoxazole-trimethoprim may also increase the anticoagulant effect by inhibiting the metabolism of the anticoagulant by trimethoprim[23] or by increasing the plasma concentration of free coumarin by sulfamethoxazole.[24] The degree of inhibition of the metabolism may be different for acenocoumarol and phenprocoumon.[20] The results of our study are in agreement with this theory. The underlying indication, fever, and other illness-related factors may also be responsible for an increase in the anticoagulant effect when antibacterial drugs are used. After we adjusted for these potential confounders, doxycycline was no longer associated with overanticoagulation. Amoxicillin plus clavulanic acid, however, remained a risk

Table II. Potentially interacting drugs and drug classes used by at least 10 patients

Drug (class)	*No. of users*	*No. of users with a relevant* change in use*
Acetaminophen (INN, paracetamol)	179	124
HMG-CoA reductase inhibitors	156	7
Simvastatin	93	1
Pravastatin	25	2
Fluvastatin	13	0
Atorvastatin	27	4
Cerivastatin	2	0
Omeprazole	45	6
Tetracyclines	43	40
Doxycycline	41	38
Tetracycline	1	1
Minocycline	1	1
Biguanides; metformin	33	0
Penicillins	26	26
Amoxicillin (INN, amoxicilline)	16	16
Amoxicillin plus clavulanic acid	10	10
Amiodarone	25	3
Ranitidine	23	4
Sulfamethoxazole-trimethoprim	22	19
Thyroxines	20	0
Fibrates	18	1
Clofibrate	1	0
Gemfibrozil	13	1
Ciprofibrate	4	0
Spironolactone	14	0
Tramadol	12	6
Allopurinol	11	0
Macrolides	11	10
Clarithromycin	9	9
Azithromycin	2	1

HMG-CoA, 3-Hydroxy-3-methylglutaryl coenzyme A
*Start, dose increase, or irregular and infrequent use (ie, 1 or 2 times a week) of an interacting drug enhancing the anticoagulant effect or discontinuation dose reduction, or irregular and infrequent use of an interacting drug diminishing the anticoagulant effect

Table III. Association between overanticoagulation (INR ≥6.0) and changes in drug use*

Variable	*Case patients (n = 300)*	*Control subjects (n = 302)*	*OR [95%CI], univariate*	*OR [95%CI], multivariate*
Antibacterial drugs				
Sulfamethoxazole-trimethoprim	18	1	19.2 [2.6-144.5]	24.2 [2.8-209.1]†
Amoxicillin	10	6	1.7 [0.6-4.7]	
Amoxicillin plus clavulanic acid	8	2	4.1 [0.9-19.2]	5.1 [0.6-46.6]†
Doxycycline	26	12	2.3 [1.1-4.6]	1.4 [0.6-3.6]†
Ciprofloxacin	3	0	$P = .50$	
Norfloxacin	1	2	0.5 [0.0-5.6]	
Clarithromycin	5	4	1.3 [0.3-4.7]	
Analgesics				
Acetaminophen	71	53	1.5 [0.98-2.2]	1.2 [0.7-2.0]†
Salicylates >300 mg	2	3	0.7 [0.1-4.0]	
Tramadol	5	1	5.0 [0.6-42.3]	
Gastrointestinal drugs				
Ranitidine	1	3	0.3 [0.0-3.2]	
Omeprazole	2	4	0.5 [0.1-2.8]	
HMG-CoA reductase inhibitors				
Atorvastatin	3	1	3.0 [0.3-29.3]	
Antiarrhythmic agents				
Amiodarone	3	0	$P = .12$	
Vitamin supplements	4	4	1.0 [0.2-4.0]	

INR International normalized ratio

*Values are numbers. Those drugs for which the number of patients with a relevant change in use was less than 3 are not included in the table. This concerns tetracycline (1 case patient/0 control subjects), minocycline (0/1), azithromycin (0/1), cefaclor (0/1), ceftibuten (0/1), piroxicam (1/0), cisapride (1/0), simvastatin (0/1), pravastatin (0/2), gemfibrozil (1/0), cholestyramine (INN colestyramine) (1/0) carbamazepine (1/0) phenytoin (1/0), miconazole (1/1), fluoxetine (0/2), chlorthalidone (INN chlortalidone) (0/1) metronidazole (1/0).

†Sulfamethoxazole-trimethoprim amoxicillin plus clavulanic acid, doxycycline, acetaminophen, age, sex, the number of INR determinations in the preceding 3 months, fever diarrhea, relapse of congestive heart failure, illness of the urinary tract, change in weight and change in alcohol consumption were included in the model.

factor. This difference may be caused by a difference in effect on the intestinal microflora.

To our knowledge, epidemiologic studies on risk factors for overanticoagulation in a nonselected population under everyday circumstances are scarce and were only published for the first time in 1998. Two of 3 earlier studies[25,26] have some limitations. The third study[27] was well performed; however, changes in drug use were not studied individually. Newly started treatment with potentiating drugs (all combined, half of which were antibiotics) and the use of acetaminophen were independent determinants of an INR value ≥6.0. The latter finding is in contrast with our study. This may possibly be because we used a 4-week risk period, whereas that study[27] used only the preceding week as a potential risk period. Another difference between the study of Hylek et al[27] and our study is that the study population of Hylek et al[27] used warfarin, whereas our patients used phenprocoumon or acenocoumarol. In addition, we included only stable case patients and control subjects. Finally, potential confounding by a change in weight, physical activity, or alcohol consumption was not taken into account in the study of Hylek et al.[27]

In conclusion, in this study among previously stable outpatients of an anticoagulation clinic using phenprocoumon or acenocoumarol, drug interactions as a cause of overanticoagulation predominantly concerned antibacterial drugs. If possible, the use of sulfamethoxazole-trimethoprim and amoxicillin plus clavulanic acid should be avoided in patients taking coumarins. If there is no therapeutic alternative available, increased monitoring of INR values is warranted to prevent overanticoagulation and potential bleeding complications.

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