Eur J Clin Pharmacol (2007) 63:335–343
DOI 10.1007/s00228-007-0268-6

PHARMACODYNAMICS

Coumarin anticoagulants and co-trimoxazole: avoid the combination rather than manage the interaction

Tom Schalekamp · Johanna H. H. van Geest-Daalderop · Mark H. H. Kramer · Angelique T. M. van Holten-Verzantvoort · Anthonius de Boer

Received: 5 November 2006 / Accepted: 18 January 2007 / Published online: 21 February 2007

Abstract
Objective The objective of our study was to examine the management of the interaction between acenocoumarol or phenprocoumon and several antibiotics by anticoagulation clinics and to compare the consequences of this interaction on users of co-trimoxazole with those for users of other antibiotics.
Methods A follow-up study was conducted at four anticoagulation clinics in The Netherlands. Data on measurements of the International Normalised Ratio (INR), application of a preventive dose reduction (PDR) of the coumarin anticoagulant, fever and time within or outside the therapeutic INR range were collected.
Results The study cohort consisted of 326 subjects. A PDR was given more often to users of co-trimoxazole PDR than to users of other antibiotics. The PDR in co-trimoxazole users resulted in a significantly reduced risk of both moderate overanticoagulation (INR >4.5) and severe overanticoagulation (INR >6.0) compared with no PDR, with odds ratios (ORs) of 0.06 [95% confidence interval (CI): 0.01–0.51] and 0.09 (95% CI: 0.01–0.92), respectively. In co-trimoxazole users without PDR, the risk of overanticoagulation was significantly increased compared with users of other antibiotics. All co-trimoxazole users spent significantly more time under the therapeutic INR range during the first 6 weeks after the course than users of other antibiotics.
Conclusion PDR is effective in preventing overanticoagulation in co-trimoxazole users, but results in a significantly prolonged period of underanticoagulation after the course. Avoidance of concomitant use of co-trimoxazole with acenocoumarol or phenprocoumon seems to be a safer approach than management of the interaction between these drugs.

Keywords Acenocoumarol · Antibiotics · Anticoagulation clinic · Co-trimoxazole · Coumarins · Drug interaction · Phenprocoumon

T. Schalekamp · A. de Boer
Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute of Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, Utrecht, The Netherlands

J. H. H. van Geest-Daalderop
Thrombosis Service, Department of Laboratory of Clinical Chemistry and Haematology, Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands

M. H. H. Kramer
Thrombosis Service Eemvallei, Amersfoort, The Netherlands

A. T. M. van Holten-Verzantvoort
Thrombosis Service het Gooi, Hilversum, The Netherlands

T. Schalekamp (✉)
Department of Pharmacoepidemiology and Pharmacotherapy, Faculty of Pharmaceutical Sciences, P.O. Box 80082, 3508 TB Utrecht, The Netherlands
e-mail: t.schalekamp@pharm.uu.nl

Introduction

Coumarin-type anticoagulants have a narrow therapeutic range. One important aspect of their safety is their sensitivity to drug interactions, many of which have been described [9, 11].

There are several reasons why antibiotic use can be considered to be indicative of a change in anticoagulation status in users of coumarin-type anticoagulants. When the

antibiotic is used for febrile illness, it may be associated with overanticoagulation [5, 12]. In two studies on the interaction between coumarin anticoagulants and antibiotics, the risk of severe overanticoagulation, defined as an International Normalised Ratio (INR) ≥6.0, was increased more in users of sulfamethoxazole-trimethoprim (co-trimoxazole) than in users of other antibiotics [12, 21]. Sulfamethoxazole is a strong inhibitor of CYP2C9 [24], the main liver enzyme involved in the metabolism of warfarin [13], acenocoumarol [19] and probably phenprocoumon [20], which could explain this stronger association with overanticoagulation. Current clinical guidelines in The Netherlands for the management of coumarin drug interactions advise healthcare givers to avoid prescribing the concurrent use of co-trimoxazole and coumarins [1]. Nevertheless, in daily practice co-trimoxazole is frequently prescribed to users of coumarins, since physicians in anticoagulation clinics assume that an interaction with co-trimoxazole can be managed in a manner similar to those used to manage interactions that arise with the concurrent use of coumarins with other antibiotics. An anticoagulation clinic will initiate one of the following procedures once it has been notified of the initiation of the use of an antibiotic: (1) measurement of the INR during the antibiotic course and adjustment of the coumarin dose depending on the INR value (a *reactive* dose-adjustment); (2) a preventive (coumarin) dose reduction (PDR) preceding an INR measurement during or after the antibiotic course, assuming that use of an antibiotic or the intercurrent infection itself increases the risk of overanticoagulation. The PDR approach seems even more relevant to co-trimoxazole than to other antibiotics because the CYP2C9-inhibiting effect of the former might increase the risk of overanticoagulation more than the infectious state alone. However, PDR could also lead to temporary undertreatment, and evidence for the effectiveness of this approach is currently lacking. There are no official guidelines for such dose adjustments, and the application of PDR strongly depends on the personal view of the responsible physician.

The aim of the present study was to examine the management of the interaction between coumarin anticoagulants and antibiotics by anticoagulation clinics and its consequences for users of co-trimoxazole and other antibiotics. To this end, we conducted a prospective follow-up study at four anticoagulation clinics in The Netherlands.

Materials and methods

Study design

This was a follow-up study conducted at four anticoagulation clinics in The Netherlands. We included patients who were stabilised on one of the coumarin anticoagulants acenocoumarol or phenprocoumon and who had started using one of the following antibiotics between January 2001 and October 2003: co-trimoxazole, amoxicillin, amoxicillin-clavulanic acid, clarithromycin, doxycyclin, nitrofurantoin, norfloxacin or trimethoprim. In addition to co-trimoxazole, we chose the other antibiotics based on their use for the same kind of infections, mainly those of the urinary and respiratory tract.

The subjects included in our study were prospectively followed during the antibiotic course until the last INR measurement, which occurred within 6 weeks following the starting date of the antibiotic (follow-up time). We did not intervene in the daily routine of the participating anticoagulation clinics and, in particular, we made no agreements on checking the INR of patients during the antibiotic course, on making additional INR measurements, on the time intervals between INR measurements after the antibiotic courses or on dose adjustments when antibiotics were prescribed. To assess the consequences of interaction management reliably and to avoid confounding by an unstable anticoagulation status preceding the antibiotic course, we only included stabilised patients in our study. Criteria for the assessment of stability were: (1) use of the coumarin anticoagulant for at least 50 days before initiation of the antibiotic; (2) availability of at least four INR measurements before the initiation of the antibiotic; (3) the last two INR measurements before initiation of the antibiotic were within the therapeutic range; (4) a maxim of one out of the last four INR measurements or a maxim of 30% of the INR measurements during the 50 days immediately preceding initiation of the antibiotic were outside of the therapeutic range, with no INR being above 5.5. Similar criteria for stability have been used in other studies [12, 21].

We excluded subjects from our analyses in whom the INR was not measured during the course of the antibiotic and who used the antibiotic for a period shorter than 3 days and longer than 14 days. If the INR was not measured during the course, an interaction effect of the antibiotic could be missed. Antibiotics used for less than 3 days or more than 14 days are usually prescribed for prophylaxis not for acute infections.

All patients were informed of the aims of the study and were asked for their *written* consent to participate in the study.

Setting and attitudes of anticoagulation clinics on antibiotic use

All anticoagulation clinics in The Netherlands monitor the INR in outpatients at a frequency varying from a few days to maximally 6 weeks. The two target therapeutic ranges

are the normal therapeutic range (INR: 2.0–3.5) and the high therapeutic range (INR: 2.5–4.0).

The initiation of the use of an antibiotic is usually reported to the anticoagulation clinics by the patients, their pharmacists and/or the prescribing physicians.

The four anticoagulation clinics participating in this study had different attitudes on the management of the interaction between coumarins and antibiotics. The approach of three of the anticoagulation clinics was to decrease the coumarin dose preventively if co-trimoxazole was prescribed; one of the anticoagulation clinics applied a PDR of 20–25% in the case of co-trimoxazole use. If one of the other antibiotics examined in this study was prescribed, the application of a PDR would depend on the seriousness of the disease and on the occurrence of fever. The fourth anticoagulation clinic had no established protocols for dose reduction but indicated that it would monitor the INR of every user of co-trimoxazole within 3–5 days after initiation of the course.

Data collection

We collected relevant data on the participating patients and recorded these in a database: sex and age of patient; dosage and indication of the coumarin; prescribed antibiotics (indication, dosage and duration of use); results of INR measurements before, during and after the antibiotic course; co-medication; relevant co-morbidities (malignancies, thyroid diseases, heart failure). These data were retrieved from the medical files of the anticoagulation clinics. Patients were asked to indicate on a questionnaire for which infection the antibiotic was prescribed and whether they had suffered from fever during the antibiotic course. We recorded this as fever yes/no in our database. If the coumarin-dose was reduced as soon as the antibiotic was started in the absence of an actual INR, we recorded this as a *preventive* dose-reduction and calculated the percentage of the dose reduction from the data on dosage in the file of the anticoagulation clinic.

In order to assess the anticoagulation status shortly *after* the antibiotic course, we recorded the time spent within, above and under the therapeutic range from the starting date of the antibiotic until the last INR measurement within 6 weeks following the starting date of the antibiotic. Six weeks is the maximal period between two INR measurements if a patient is well stabilised. Furthermore, after a longer follow-up period, differences between patients could be more attributable to other factors than to the infection or antibiotic use. If after the first INR during the antibiotic course no second INR measurement was available within the 6-week period after the starting date of the antibiotic, we recorded no follow-up time and no time spent within, above or under the therapeutic range.

Outcomes

The end points of our study were chosen to assess the effectiveness of the management of the interaction between coumarin anticoagulants and co-trimoxazole and other antibiotics.

We examined the following parameters in users of co-trimoxazole with and without PDR as well as in users of other antibiotics with and without PDR:

1. occurrence of moderate overanticoagulation (INR >4.5) and severe overanticoagulation (INR >6.0);
2. time spent within, above and under the therapeutic INR range from the starting date of the antibiotic until the last INR measurement within 6 weeks following the starting date of the antibiotic.

Calculations and statistical analysis

We assessed the effects of the PDR within the group of users of co-trimoxazole and within the group of users of other antibiotics by comparing the occurrence of overanticoagulation in patients for whom a PDR had been applied with the occurrence of overanticoagulation in patients for whom PDR had not been applied (logistic regression models). We also compared the occurrence of overanticoagulation and time spent within, under and above the therapeutic range of co-trimoxazole users with users of other antibiotics (reference group). These comparisons were made for patients with PDR and for patients without PDR. Finally, we compared the time spent within, under and above the therapeutic range in patients for whom a PDR had been applied with those for whom a PDR had not been applied (reference) within the groups of co-trimoxazole users and users of other antibiotics (linear regression models). In all models we adjusted for the potential confounding covariates sex, age, target therapeutic range and fever, as indicated by the patient. Covariates were added to the statistical models one at a time. We adjusted for a covariate if it changed the point estimation of the outcome of interest by 5% or more upon inclusion in the model.

Time spent within, above and under the therapeutic INR range was calculated by the step-up method described by Rosendaal et al. [15].

Although all patients were stable when they were included in our study, we re-analysed our statistically significant outcomes after excluding patients in whom destabilisation could be due to factors other than those of infection and/or fever (presence of thyroid disease, malignancy or use of other enzyme-inhibiting or-inducing drugs).

All statistical analyses were performed with the statistical software package SPSS ver. 12 (SPSS, Chicago, Ill.).

Results

A total of 424 patients who met the inclusion criteria gave their informed consent to participate in our study. Of these patients, 81 did not have assesment of the INR during the antibiotic course, 14 used the antibiotic for less than 3 days, and 3 used the antibiotic for more than 14 days.

A PDR was applied more frequently for users of co-trimoxazole (28/43; 65%) than for users of other antibiotics (60/283; 21.2%) (Table 1).

The PDR applied was significantly greater in users of co-trimoxazole than in users of other antibiotics (15.0 and 10.3%, respectively; *P* value for difference: 0.036; two-sided *t*-test). The number of INR measurements during follow-up was significantly higher in both users of co-trimoxazole (PDR applied and PDR not applied) and users of other antibiotics (PDR applied) than in users of other antibiotics in whom a PDR was not applied. (*P* values of 0.028, 0.006 and 0.007, respectively; two-sided *t*-test). Mean daily dosages for acenocoumarol were lower in users of co-trimoxazole than in users of other antibiotics, but this difference was not statistically significant and even smaller (0.14 mg) after adjustment for differences in age (Table 1).

In co-trimoxazole users, the PDR protected strongly against both moderate and severe overanticoagulation [adjusted odds ratio (OR): 0.06, 95% confidence interval (CI): 0.01–0.51 for INR >4.5; adjusted OR: 0.09, 95% CI: 0.01–0.92 for INR >6]. For other antibiotics, the effect of the PDR on overanticoagulation was not as strong and not statistically significant (Tables 2 and 3).

If PDR was applied, the risk of overanticoagulation was not increased in users of co-trimoxazole compared with users of other antibiotics. However, if PDR was not applied, there was a strongly increased risk of moderate as well as severe overanticoagulation in co-trimoxazole users compared with users of other antibiotics (adjusted OR: 3.96, 95% CI: 1.33–11.8 for INR >4.5; adjusted OR: 3.86, 95%CI: 1.03–14.6 for INR >6.0) (Tables 2 and 3).

During the 6-week follow-up, co-trimoxazole users with a PDR spent more time within and less time under the therapeutic range than co-trimoxazole users without a PDR, but these differences were not statistically significant. Users of co-trimoxazole without a PDR spent significantly less time within the therapeutic range than users of other antibiotics with a PDR, whereas significantly more time was spent under the therapeutic range. Moreover, co-trimixazole users with a PDR also spent significantly more time under the therapeutic range than did all users of other

Table 1 Characteristics of patients (n = 326) using antibiotics, treated by four anticoagulation clinics

Characteristic	Co-trimoxazole (n=43)		Other antibiotics[a] (n=283)	
	PDR+[b] (n=28)	PDR-[c] (n=15)	PDR+[b] (n=60)	PDR-[c] (n=223)
Men, no. (%)	22 (78.6)	10 (66.7)	30 (50.0)	114 (51.1)
Age in years, mean (SD)	75.4 (10.9)	75.1 (8.2)	72.6 (10.9)	71.4 (11.2)
Users of acenocoumarol, no. (%)	24 (85.7)	10 (66.7)	52 (86.7)	169 (75.8)
Follow-up time, mean (SD)	33.2 (5.6)	28.9 (8.0)	30.4 (7.2)	30.2 (7.2)
Fever, no. (%)	18 (64.3)	6 (40.0)	27 (45.0)	120 (53.8)
Normal target therapeutic range, no. (%)[d]	19 (67.9)	5 (33.3)	30 (50.0)	112 (50.2)
Respiratory infections, no. (%)	8 (28.6)	3 (20.0)	33 (55.0)	116 (52.0)
Urinary tract infections, no. (%)	13 (46.4)	8 (53.3)	11 (18.3)	53 (23.8)
Malignancies, no. (%)	1 (3.6)	3 (20.0)	3 (5.0)	9 (4.0)
Thyroid diseases, no. (%)	0	0	1 (1.7)	11 (4.9)
Users of inhibiting drugs, no. (%)	0	1 (6.7)	5 (8.3)	17 (7.6)
Users of inducing drugs, no. (%)	1 (3.6)	0	1 (1.7)	4 (1.8)
INR measurements, mean no. (SD)	3.5 (0.9)	3.9 (1.5)	3.5 (1.1)	3.1 (1.1)
Acenocoumarol, mean dose, mg/day (SD)	2.42 (1.26)	2.41 (1.41)	2.61 (1.06)	2.60 (1.12)
Percentage PDR applied, mean (SD) in acenocoumarol users	15.0 (7.6)		10.3 (11.1)	
Phenprocoumon, mean dose, mg/day (SD)	2.81 (0.86)	2.53 (1.02)	2.99 (1.31)	2.36 (1.00)
Percentage PDR applied, mean (SD) in phenprocoumon users	17.9 (15.8)		11.4 (7.0)	
Percentage PDR applied, all coumarins, mean (SD)	15.4 (8.8)		10.5 (10.6)	

[a] Other antibiotics: Trimethoprim (n=3), doxycyclin (n=104), amoxicillin (n=77), amoxicillin-clavulanic acid (n=36), clarithromycin (n=14), norfloxacin (n=33), nitrofurantoin (n=16)
[b] PDR+, Preventive dose reduction applied
[c] PDR-, Preventive dose reduction not applied
[d] Normal target therapeutic range: INR 2.0–3.5

Table 2 Occurrence of overanticoagulation and time spent within, above and under the therapeutic range by patients using co-trimoxazole and other antibiotics[a]

Outcome	Co-trimoxazole		Other antibiotics	
	PDR+[b] (n=28)	PDR-[b] (n=15)	PDR+[b] (n=60)	PDR-[b] (n=223)
INR >4.5, no. (%)	3 (10.7)	25 (89.3)	9 (15.0)	45 (20.2)[d]
INR > 6.0, no. (%)	1 (3.6)	4 (26.7)	5 (8.3)	14 (6.3)[e]
Time within therapeutic range, mean % (95%CI)[c]	71.1 (60.4–81.8)	51.8 (34.6–69.0)	76.2 (69.5–82.9)	75.7 (72.2–79.3)[f]
Time above therapeutic range, mean % (95%CI)	15.0 (5.7–24.3)	20.3 (10.7–29.8)	12.3 (6.8–17.7)	18.9 (15.5–22.2)[g]
Time under therapeutic range, mean % (95%CI)	14.0 (5.6–22.2)	27.9 (7.7–48.1)	11.5 (6.9–16.1)	5.4 (3.7–7.2)[h]

[a] Calculated for the time from the date the antibiotic was first taken until the last INR measurement within 6 weeks following the starting date of the antibiotic. Time within, above and under therapeutic range was calculated for antibiotic users in whom at least one INR measurement had been performed within 6 weeks after the INR measurement during the antibiotic course. This resulted in the exclusion from the analysis of the following number of subjects: co-trimoxazole (1 1); other antibiotics 14 (1 13). The numbers in parenthesis indicate the number of subjects with a PDR and those without a PDR, respectively.
[b] PDR+, Preventive dose reduction applied; PDR-, preventive dose reduction not applied.
[c] 95% CI, 95% Confidence interval for the reported mean value
[d] Range: 7.1% for nitrofurantoin to 27.6% for norfloxacin
[e] Range: 0% for nitrofurantoin and trimethoprim to 8.6% for doxycyclin
[f] Range: 71.8% for amoxicillin to 84.8% for norfloxacin
[g] Range: 8.6% for norfloxacin to 22.0% for amoxicillin
[h] Range: 3.3% for norfloxacin to 11.1% for clarithromycin

antibiotics (adjusted mean difference: 6.9%; 95%CI: 1.0–12.9) (Tables 2 and 4).

Co-trimoxazole users with more than a 20% PDR spent significantly more time under the therapeutic range than users of other antibiotics (adjusted mean difference: 7.4 mg; 95%CI: 0.9–14.0; P=0.027). If less than a 20% PDR was applied, the difference between the users of co-trimoxazole and those of other antibiotics shrunk and was no longer significant.

The application of a PDR differed between anticoagulation clinics. Three of the four anticoagulation clinics

Table 3 Odds ratios for effect of preventive dose reduction (PDR) and for (severe) overanticoagulation in users of co-trimoxazole compared with users of other antibiotics

	Odds ratios (95%CI)	P	Adjusted Odds ratios (95% CI)[a]	P
Effect of PDR on overanticoagulation[b]				
Co-trimoxazole				
PDR applied, INR >4.5	0.10 (0.02–0.50)	0.005*	0.06 (0.01–0.51)	0.010*
PDR applied, INR >6.0	0.10 (0.01–1.02)	0.051	0.09 (0.01–0.92)[c]	0.042*
PDR not applied	Reference		Reference	
Other antibiotics				
PDR applied, INR >4.5	0.70 (0.32–1.52)	0.37	N.A.[d]	
PDR applied, INR >6.0	1.36 (0.47–3.93)	0.57	N.A	
PDR not applied	Reference			
Risk of overanticoagulation				
PDR not applied				
Co-trimoxazole, INR >4.5	4.52 (1.56–13.1)	0.006*	3.96 (1.33–11.8)	0.013*
Co-trimoxazole, INR >6.0	5.43 (1.53–19.2)	0.009*	3.86 (1.03–14.6)	0.046*
Other antibiotics	Reference		Reference	
PDR applied				
Co-trimoxazole, INR >4.5	0.68 (0.17–2.73)	0.59	N.A.	
Co-trimoxazole, INR >6.0	0.41 (0.04–3.66)	0.42	0.30 (0.03–3.05)[e]	0.30
Other antibiotics	Reference		Reference	

*Statistically significant difference at $P \leq 0.05$
[a] Adjusted for differences in fever as indicated by patient, age, sex, target therapeutic range, unless otherwise indicated
[b] PDR, Preventive dose reduction
[c] Adjusted for differences in age and sex
[d] N.A., Adjustment not applied because the inclusion of covariates in our model did not result in a change of at least 5% in the odds ratios (see text)
[e] Adjusted for differences in age, sex and fever as indicated by patient

Table 4 Comparisons of time spent within, under and above the therapeutic range by users of co-trimoxazole and other antibiotics[a]

	Mean difference	*P*	Adjusted mean difference[b]	*P*
PDR applied				
Co-trimoxazole, % time within TR[c]	−5.1 (−17.2 to 6.9)	0.40	−4.2 (−17.1 to 8.6)	0.51
Co-trimoxazole, % time above TR	2.7 (−7.3 to 12.7)	0.60	1.9 (−8.9 to 12.7)	0.73
Co-trimoxazole, % time under TR	2.4 (−6.3 to 11.1)	0.58	N.A.[d]	
Other antibiotics	Reference		Reference	
PDR not applied				
Co-trimoxazole, % time within TR	−23.8 (−38.2 to –9.6)	< 0.001*	−22.3 (−36.6 to –8.0)[e]	0.002*
Co-trimoxazole, % time above TR	1.4 (−11.7 to 14.5)	0.83	N.A.	
Co-trimoxazole, % time under TR	22.5 (14.4 to 30.6)	< 0.001*	20.4 (12.4 to 28.5)[f]	< 0.001*
Other antibiotics	Reference		Reference	
Co-trimoxazole				
PDR applied, % time within TR	19.3 (0.7 to 37.9)	0.042*	14.6 (−5.8 to 35.1)[f]	0.16
PDR applied, % time above TR	−5.3 (−19.6 to 9.0)	0.46	−4.4 (−19.1 to 10.3)[g]	0.55
PDR applied, % time under TR	−14.0 (−31.6 to 3.6)	0.16	−10.7 (−29.0 to 7.5)[g]	0.24
PDR not applied	Reference		Reference	
Other antibiotics				
PDR applied, % time within TR	0.5 (−7.0 to 8.1)	0.89	0.6 (−6.8 to 8.2)	0.87
PDR applied, % time above TR	−6.6 (−13.5 to 0.3)	0.061	N.A.	
PDR applied, % time under TR	6.1 (2.0 to 10.1)	0.003*	N.A.	
PDR not applied	Reference		Reference	
Co-trimoxazole, PDR applied				
% time within TR	−4.7 (−15.1 to 5.6)	0.37	−3.0 (−13.5 to 7.5)[f]	0.58
% time above TR	−2.4 (−11.9 to 7.1)	0.61	−3.7 (−13.3 to 6.0)[h]	0.46
% time under TR	7.2 (1.2 to 13.1)	0.018*	6.9 (1.0 to 12.9)[h]	0.022*
Other antibiotics				
PDR applied + PDR not applied	Reference		Reference	

*Statistically significant difference at $P \leq 0.05$

[a] Calculated for the time from the starting date of the antibiotic until the last INR measurement within 6 weeks following the starting date of the antibiotic.

[b] Adjusted for differences in fever as indicated by patient, age, sex, target therapeutic range, unless otherwise indicated.

[c] TR, Therapeutic range;

[d] N.A., Adjustment not applied because including covariates in our model did not result in a change of at least 5 % of mean difference (see text).

[e] Adjusted for differences in sex.

[f] Adjusted for differences in sex and target therapeutic range.

[g] Adjusted for differences in age, sex and target therapeutic range.

[h] Adjusted for differences in sex, target therapeutic range and fever as indicated by patients.

participating in this study applied PDR as a rule in co-trimoxazole users (83.3–85.7%). In terms of users of other antibiotics, the application of a PDR was more varied: in three of the anticoagulation clinics PDR was sometimes applied (in 17.6–50.8% of all cases), whereas one anticoagulation clinic did not apply the PDR approach at all. The overall percentage of time spent within the therapeutic range during the first 6 weeks after initiation of an antibiotic ranged from 73.7 to 78.0% at all four anticoagulation clinics. In the anticoagulation clinic that did not apply a PDR, overanticoagulation (INR>4.5) occurred most frequently for the all antibiotics class (26.9 vs.10.8–22.7% in the other clinics), with the difference being most marked for co-trimoxazole (54.4 vs. 14.3–16.7% in the other clinics).

We also analysed our data separately for users of acenocoumarol and phenprocoumon. There were no differences in the point estimates of most of our main outcomes between users of either of these coumarins, with the exception of percentage of time spent under the therapeutic range in phenprocoumon users for whom PDR was applied. However, most of the results that were statistically significant for all coumarin users were also significant for users of acenocoumarol (n=252; 78.2 %), whereas they were in most cases not significant for the smaller group of users of phenprocoumon (n=71; 21.8%) (Table 5).

Re-analysis of our results after excluding patients with thyroid diseases and malignancy or those using enzyme-inhibiting or -inducing drugs gave similar point estimates or trends, significance for severe overanticoagulation in users of co-trimoxazole compared to other antibiotics and for time spent within the therapeutic range for users of co-trimoxazole in whom PDR was not applied (data not shown).

Table 5 Main outcomes stratified for users of acenocoumarol and phenprocoumon

Outcome	Acenocoumarol (n=254)		Phenprocoumon (n=71)	
Protective effect of PDR	Adjusted OR (95%CI)[a]	P	Adjusted OR (95%CI)[a]	P
Co-trimoxazole				
PDR applied, INR >4.5	0.08 (0.01–0.70)	0.022*	0.16 (0.01–4.48)	>0.3[b]
PDR not applied	Reference		Reference	
Risk of overanticoagulation				
PDR not applied				
Co-trimoxazole, INR >4.5	4.40 (1.15–16.8)	0.030*	3.83 (0.55–26.7)	0.18
Other antibiotics	Reference		Reference	
% Time within or under TR	Mean difference (95%CI)		Mean difference (95%CI)	
Co-trimoxazole, % time within TR	−22.1 (−39.1 to −5.0)	0.011*	−21.4 (−49.4 to 6.6)	0.13
Co-trimoxazole, % time under TR	20.3 (10.9–29.7)	<0.001*	22.6 (5.7–39.5)	0.010*
Other antibiotics	Reference		Reference	
Co-trimoxazole, PDR applied				
% time under TR	9.1 (3.0–15.1)	0.004*	−6.7 (−23.0 to 9.6)	0.42
Other antibiotics				
PDR applied + PDR not applied	Reference		Reference	

*Statistically significant difference at $P \leq 0.05$

[a] Adjusted for differences in fever as indicated by patient, age, sex and target therapeutic range

[b] Adjustment not applied because the number of patients with INR >4.5 was zero; OR was calculated by increasing the values of each of the cells of the crosstable by 0.5

Discussion

The results of the present study, in which we evaluated the management of the interaction between antibiotics and coumarin anticoagulants by anticoagulation clinics, demonstrated that a PDR reduces the risk of overanticoagulation in co-trimoxazole users to the level of other antibiotic users, but also that management of the interaction between coumarins and co-trimoxazole results in a significantly longer period of undertreatment during the first 6 weeks after initiation of the antibiotic.

In three of the four anticoagulation clinics PDR was applied more frequently and was significantly higher in users of co-trimoxazole than in users of other antibiotics, indicating that anticoagulation clinics are aware of the seriousness of the interaction between coumarins and co-trimoxazole. In the cases and case series that have reported on overanticoagulation and bleeding with the concurrent use of antibiotics and co-trimoxazole [2, 3, 6–8, 10] an effect of the intercurrent infection on the anticoagulation status could not be ruled out. However, Penning-van Beest et al. (case control study) and Visser et al. (follow-up study) both demonstrated that an increased risk of severe overanticoagulation (INR >6.0) was particularly associated with co-trimoxazole [12, 21]. A plausible explanation is the strong inhibition of the main metabolising enzyme, CYP2C9, of the coumarins by sulfamethoxazole, the sulphonamide component of co-trimoxazole [24].

Although PDRs as applied in clinical practice are effective in reducing the overanticoagulation risk in co-trimoxazole users, the price that has to be paid for the concurrent use of co-trimoxazole is a significantly prolonged period of underanticoagulation compared with the use of other antibiotics during the first 6 weeks after the antibiotic course. This difference was more marked in the subgroup of subjects in whom PDR was not applied. Possible explanations for this result are (1) the usually shorter time span between PDR and the first INR measurement (always within the course) compared to the time span between a reactive dose reduction following supratherapeutic INR and subsequent INR measurement (usually after the course) and (2) the higher reactive dose reduction which is applied in the case of severe overanticoagulation (INR >6.0). However, even co-trimoxazole users for whom the PDR had been applied had a significantly prolonged period of underanticoagulation compared with all of the users of other antibiotics (PDR applied and PDR not applied taken together). This last comparison is totally logical because our results strongly suggest that a PDR should always be applied in co-trimoxazole users, whereas this is as a rule not required in users of other antibiotics. The adjusted difference in time spent under the therapeutic range – ranging from 6.9 (PDR applied) to 22.5% (PDR not applied) – corresponds to about 2–7 days of the mean follow-up time of 30 days in otherwise stabilised patients; this time interval is clinically relevant and can be avoided by substituting co-trimoxazole.

It is not difficult to explain the prolonged period of underanticoagulation in co-trimoxazole users. The application of a PDR, which was in this study higher in

co-trimoxazole users, might overcompensate for over-anticoagulation, whereas the reactive dose reduction following overanticoagulation carries the same risk of overcompensation and undertreatment as PDR. Consequently, the inhibition of CYP2C9 by co-trimoxazole superimposes an additional problem upon the already potentially destabilising effects of the infection and fever. Because our results for acenocoumarol in the separate analyses were predominantly in agreement with the overall results, our findings primarily apply to acenocoumarol users. It is possible that users of phenprocoumon are less sensitive to interactions with CYP2C9 inhibitors such as co-trimoxazole [20, 22]. We do expect that our results also apply to users of warfarin, which seems to be even more CYP2C9 sensitive than acenocoumarol [18].

Our study has several limitations. Because we retrieved medical data from anticoagulation clinics, it is possible that not all of the relevant data on potentially destabilising factors, such as malignancies, thyroid diseases and the use of other inhibitors of coumarin metabolism, were available. However, by only including patients who were obviously stable at the moment of initiation of the antibiotic, we decreased the chance that such factors changed the anticoagulant status during the antibiotic course. A second limitation is the absence of data on the presence of polymorphisms of the genes encoding the coumarin-metabolising enzyme CYP2C9 or the pharmacodynamic target of coumarins, VKORC1. The genotypes of both *CYP2C9* [16, 22] and *VKORC1* are strongly associated with interindividual variability in coumarin dose requirements [4, 14, 17, 23]. Further studies would be needed to assess whether the risk of overanticoagulation in co-trimoxazole users differs between carriers of a *CYP2C9* or *VKORC1* polymorphism and wild-type patients. It should be clear that our results only apply to patients with a stabilised anticoagulation state at the initiation of the antibiotic course.

In conclusion, if co-trimoxazole is prescribed to users of coumarin anticoagulants, the interaction can be managed by applying PDR, which adequately decreases the risk of overanticoagulation, but this successful management comes at the cost of a prolonged period of underanticoagulation after the course. Consequently, rather than managing the interaction it is better to avoid prescribing co-trimoxazole as a therapeutically equivalent alternative is always available.

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