PHARMACODYNAMICS

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

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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

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) $\geq 6.0$, 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 antibody 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 assessment 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- (n=15)                     | PDR\(b\) (n=60) | PDR- (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 (0.0)               | 0 (0.0)                         | 1 (1.7)         | 11 (4.9)     |
| Users of inhibiting drugs, no. (%)            | 0 (0.0)               | 1 (6.7)                         | 5 (8.3)         | 17 (7.6)     |
| Users of inducing drugs, no. (%)              | 1 (3.6)               | 0 (0.0)                         | 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) | 10.0 (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
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 2 Occurrence of overanticoagulation and time spent within, above and under the therapeutic range by patients using co-trimoxazole and other antibiotics

| Outcome                  | Co-trimoxazole | Other antibiotics |
|--------------------------|----------------|------------------|
| PDR+ (n=28)              | PDR- (n=15)    | PDR+ (n=60)      | PDR- (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)$^f$  |
| Time within therapeutic range, mean % (95%CI)$^g$ | 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)$^h$ | 15.0 (5.7–24.3) | 20.3 (10.7–29.8) | 12.3 (6.8–17.7) | 18.9 (15.5–22.2)$^l$ |
| Time under therapeutic range, mean % (95%CI)$^i$ | 14.0 (5.6–22.2) | 27.9 (7.7–48.1) | 11.5 (6.9–16.1) | 5.4 (3.7–7.2)$^b$ |

* 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 (11); other antibiotics 14 (113). 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.

### 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

| Outcome                  | 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            |       |                                  |       |
| 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            |       |                                  |       |
| 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            |       |                                  |       |

*Statistically significant difference at P≤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
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 anti-
cogulation 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 anti-
cogulation 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 differ-
ences 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-
harming 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 4 Comparisons of time spent within, under and above the therapeutic range by users of co-trimoxazole and other antibiotics

|                               | 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    |
| % time above TR               | -5.3 (−19.6 to 9.0) | 0.46    | -4.4 (−19.1 to 10.3)\(^g\)    | 0.55    |
| % time under TR               | -14.0 (−31.6 to 3.6) | 0.16    | -10.7 (−29.0 to 7.5)\(^g\)    | 0.24    |
| Other antibiotics             |                 |         |                               |         |
| Co-trimoxazole, PDR applied   |                 |         |                               |         |
| % time within TR              | 0.5 (−7.0 to 8.1) | 0.89    | 0.6 (−6.8 to 8.2)             | 0.87    |
| % time above TR               | -6.6 (−13.5 to 0.3) | 0.061   | N.A.                          |         |
| % time under TR               | 6.1 (2.0 to 10.1) | 0.003*  | N.A.                          |         |
| Other antibiotics             |                 |         |                               |         |
| PDR applied + PDR not applied | Reference       |         | Reference                      |         |

\(^a\)Statistically significant difference at  \( P \leq 0.05\)
\(^b\)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.
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 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 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. 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

### Table 5 Main outcomes stratified for users of acenocoumarol and phenprocoumon

| Outcome                          | Acenocoumarol (n=254) | Phenprocoumon (n=71) |
|----------------------------------|-----------------------|---------------------|
| **Protective effect of PDR**     |                       |                     |
| Co-trimoxazole                   |                       |                     |
| PDR applied, INR >4.5            | Adjusted OR (95%CI)a   | Adjusted OR (95%CI)a |
| PDR not applied                  | 0.08 (0.01–0.70)       | 0.16 (0.01–4.48)    |
| **Risk of overanticoagulation**  |                       |                     |
| PDR not applied                  | Reference              | Reference           |
| Co-trimoxazole, INR >4.5         | 4.40 (1.15–16.8)       | 3.83 (0.55–26.7)    |
| 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) | −21.4 (−49.4 to 6.6) |
| Co-trimoxazole, % time under TR  | 20.3 (10.9–29.7)       | 22.6 (5.7–39.5)     |
| Other antibiotics                | Reference              | Reference           |
| Co-trimoxazole, PDR applied      | 9.1 (3.0–15.1)         | −6.7 (−23.0 to 9.6) |
| Other antibiotics                | Reference              | Reference           |
| % time under TR                  | 0.004*                 | 0.010*              |
| Co-trimoxazole, PDR applied + PDR not applied | Reference | Reference |
| Other antibiotics                | 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.
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. Conse-
sequently, 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 acenocou-
marol 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-meta-
bolising enzyme CYP2C9 or the pharmacodynamic target of
coumarins, VKORC1. The genotypes of both CYP2C9 [16,
22] and VKORC1 are strongly associated with interindivid-
ual 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 interac-
tion it is better to avoid prescribing co-trimoxazole as a
therapeutically equivalent alternative is always available.

References

1. Anonymous (2003) Standaard Afhandeling Cumarine Interacties. Available at: http://www.fnt.nl, 2003
2. Chafin CC, Ritter BA, James A, Self TH (2000) Hospital admission due to warfarin potentiation by TMP-SMX. Nurse Pract 25(12):73–75
3. Cook DE, Ponte CD (1994) Suspected trimethoprim/sulphame-
thsulphoxide-induced hypothyrombinemia. J Pharm Pract 39
(6):589–591
4. D’Andrea G, D’Ambrosio RL, Di Perna P, Chetta M, Santacroce
R, Brancaccio V et al (2005) A polymorphism in the VKORC1
gene is associated with an interindividual variability in the dose-
anticoagulant effect of warfarin. Blood 105(2):645–649
5. Demirkan K, Stephens MA, Newman KP, Self TH (2000)
Response to warfarin and other oral anticoagulants: effects of
disease states. South Med J 93(5):448–454
6. Ercihsen C, Sondena K, Soreide JA, Andersen E, Tysvoer A,
Sondena K et al (1993) Spontaneous liver hematomas induced by
anti-coagulation therapy. A case report and review of the
literature. Hepatogastroenterology 40(4):402-406
7. Erick JK, Keys PW (1978) Co-trimoxazole and warfarin: case
report of an interaction. Am J Hosp Pharm 35(11):1399–1401
8. Greenslaw CW (1979) Drug interaction between co-trimoxazole
and warfarin. Am J Hosp Pharm 36(9):1155–1156
9. Harder S, Thurmann P (1996) Clinically important drug interac-
tions with anticoagulants. An update. Clin Pharmacokinnet 30
(6):416–444
10. Hassall C, Feetam CL, Leach RH, Meynell MJ (1975) Potentiation
of warfarin by co-trimoxazole (letter). Lancet 7945:1155–1156
11. Holbrook AM, Pereira JA, Labiris R, McDonald H, Douketis
JD, Crowther M et al (2005) Systematic overview of warfarin
and its drug and food interactions. Arch Intern Med 165
(10):1095–1106
12. Penning-van Beest FJA, van Meegen E, Rosendaal FR, Stricker
BHC (2001) Drug interactions as a cause of overanticoagulation
on phenprocoumon or acenocoumarol predominantly concern
antibacterial drugs. Clin Pharmacol Ther 69:451–457
13. Rettie AE, Korzekwa KR, Kunze KL, Lawrence RF, Eddy AC,
Aoyama T et al (1992) Hydroxylation of warfarin by human
cDNA-expressed cytochrome P-450: a role for P-4502C9 in the
transcriptional regulation and warfarin dose. N Engl J Med 352
(1):54–59
14. Rieder MJ, Reiner AP, Gage BF, Nickerson DA, Eby CS,
McLeod HL et al (2005) Effect of VKORC1 haplotypes on
transcriptional regulation and warfarin dose. N Engl J Med 352
(22):2285–2293
15. Rosendaal FR, Cannegeiter S, Meer van der FJM, Briet E (1993)
A method to determine the optimal intensity of oral anticoagulant
therapy. Thromb Haemost 69(3):236–239
16. Schalekamp T, van Geest-Daaldere JHH, de Vries-Goldschmeding
H, Cohenmans J, Berens MJ, de Boer A (2004) Acenocoumarol
stabilization is delayed in CYP2C9*3 carriers. Clin Pharmacol Ther
75(5):394–402
17. Sconce EA, Khan TI, Wynne HA, Avery P, Monkhouse L, King
BP et al (2005) The impact of CYP2C9 and VKORC1 genetic
polymorphism and patient characteristics upon warfarin dose
requirements: proposal for a new dosing regimen. Blood 106
(7):2329–2333
18. Takahashi H, Wilkinson GR, Padrini R, Echizen H (2004)
CYP2C9 and oral anticoagulation therapy with acenocoumarol
and warfarin: similarities yet differences. Clin Pharmacol Ther
75:376–380
19. Thijssen HHW, Flinois J-P, Beaune P (2000) Cytochrome
P4502C9 is the principal catalyst of racemic acenocoumarol
hydroxylation reactions in human liver microsomes Drug Metab
Dispos 28:1284–1290
20. Ufer M, Svensson JO, Krausw KW, Gelboin HV, Rane A, Tybring
G (2004) Identification of cytochromes P450 2C9 and 3A4 as the
major catalysts of phenprocoumon hydroxylation in vitro. Eur J
Clin Pharmacol 59(3):173–182
21. Visser LE, Penning-van Beest FJA, Kasbergen HAA, De Smet
PAGM, Vulto AG, Hofman A et al (2002) Overanticoagulation

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22. Visser LE, van Vliet M, van Schaik RHH, Kasbergen HAA, De Smet PAGM, Vulto AG et al (2004) The risk of overanticoagulation in patients with cytochrome P450 CYP2C9*2 or CYP2C9*3 alleles on acenocoumarol or phenprocoumon. Pharmacogenetics 14:1–7

23. Wadelius M, Chen LY, Downes K, Ghorì J, Hunt S, Eriksson N et al (2005) Common VKORC1 and GGCX polymorphisms associated with warfarin dose. Pharmacogenomics J 5(4):262–270

24. Wen X, Wang J-S, Backmann JT, Laitila J, Neuvonen PJ (2002) Trimethoprim and sulfamethoxazole are selective inhibitors of CYP2C8 and CYP2C9, respectively. Drug Metab Dispos 30 (6):631–635

associated with combined use of antibacterial drugs and acenocoumarol or phenprocoumon anticoagulants. Thromb Haemost 88:705–710