Towards improvement of oral anticoagulant therapy

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CHAPTER 3

The Relationship between Maintenance Dosages of Three Vitamin K Antagonists: Acenocoumarol, Warfarin and Phenprocoumon

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Abstract

Introduction Vitamin K antagonists of the coumarin type are widely used oral anticoagulants.

Objective We developed a transition algorithm for the maintenance dosages of three frequently used coumarins: warfarin, phenprocoumon and acenocoumarol.

Methods The study was conducted at the Leiden Anticoagulation Clinic. Patients were participants in a trial of which the main objective was to compare the quality of an oral anticoagulant therapy with phenprocoumon to warfarin. We included patients who initiated oral anticoagulant therapy and patients who were already using acenocoumarol. Patients were randomized to a treatment with warfarin or phenprocoumon. Patients who were randomized to warfarin switched to phenprocoumon at end of follow up. We analysed the switch from acenocoumarol to warfarin or phenprocoumon at start of follow up and the switch of warfarin to phenprocoumon at the end of follow up and calculated the transition factors for stable anticoagulation between these three vitamin K antagonists.

Results 58 patients switched from warfarin to phenprocoumon, 39 from acenocoumarol to phenprocoumon and 44 from acenocoumarol to warfarin. The maintenance dose of warfarin was 0.41 (95%CI 0.39- 0.43) times the maintenance dose of phenprocoumon. The transition factor between acenocoumarol and phenprocoumon was 0.84 (95%CI 0.79- 0.89) and between acenocoumarol and warfarin 1.85 (95%CI 1.78- 1.92).

Conclusions We determined the transition factors between warfarin, phenprocoumon and acenocoumarol. With these transition factors physicians are able to estimate the maintenance dose when it is necessary for a patient to switch from one coumarin to the other.

Introduction

Vitamin K antagonists of the coumarin type are widely used oral anticoagulants. They are proven to be effective in the treatment and prevention of arterial and venous thrombosis [1-3]. Worldwide there are different coumarin derivatives available. The coumarins most frequently used are warfarin, acenocoumarol and phenprocoumon. Warfarin is the coumarin of first choice in the United States of America, the United Kingdom and many other countries around the world; acenocoumarol and phenprocoumon are frequently used in many European countries. These three coumarin derivatives mainly differ in their half-life. Acenocoumarol has the shortest half-life of 11 hours, followed by warfarin with 36-42 hours and the longest half-life is seen in phenprocoumon with approximately 140 hours [4-7]. Also the clearance of these coumarins is not similar. Acenocoumarol is for its elimination completely dependent on hydroxylation by cytochrome p450 (CYP). Warfarin is also dependent on reduction processes [8]. Phenprocoumon can, in addition to elimination as hydroxylated metabolites, be eliminated as parent compound and is thus less dependent on hydroxylation by CYP. These differences in dependence on hydroxylation by the CYP enzymes offer an explanation of different responses found in studies investigating the effects of polymorphisms in the CYP2C9 gene [9,10]. Several studies have compared the different coumarins with regard to the quality of treatment, e.g. stability. Most studies have compared the short acting acenocoumarol to the longer acting warfarin or phenprocoumon. The results were mostly in favour of the longer acting coumarins, but not always [11-19].

Sometimes transition from one coumarin to another is required. Reasons to switch can be women trying to get pregnant for whom the use of phenprocoumon is contra-indicated because of its long half-life and acenocoumarol is preferred, the experience of allergic reactions or side effects such as hair loss. Coumarin

sensitivity can be a reason to switch from one coumarin to the other for practical reasons, since a maintenance dose of less than 1 mg of acenocoumarol is difficult to administer (tablets contain 1 mg, and cannot be divided). Finally, patients who are very instable are sometimes thought to benefit from switching to another coumarin derivative with a longer half-life. At present, literature about the transition from one coumarin to another is surprisingly scarce. One study investigated a dosage scheme for transition from phenprocoumon to warfarin in patients treated in an outpatients clinic [20]. The authors found that the dosage for an optimal INR of warfarin is 2.3 times the dosage of phenprocoumon. Applying this transition factor resulted in 75% of patients for whom the right dosage could be determined. No studies are known that included transition to or from acenocoumarol.

We studied the relationship between the maintenance dosages of acenocoumarol, warfarin and phenprocoumon in patients participating in a randomized controlled trial.

Methods

Study design and patient population

Patients participated in a randomized controlled trial conducted at the Leiden Anticoagulation clinic. Inclusion of patients occurred between February 2004 and April 2007. The main objective of the trial was to compare the quality of oral anticoagulant treatment with phenprocoumon versus warfarin. Follow-up was six months. Patients were eligible to participate when they were aged between 18 and 85 years and had an indication for anticoagulant treatment for at least three months. Exclusion criteria were pregnancy or intended pregnancy, renal dialysis, chemotherapy, known allergic reactions for warfarin or phenprocoumon or a contra-indication to oral anticoagulant treatment.

Two patient groups were included in the trial. The first group consisted of patients initiating oral anticoagulant treatment and was recruited in three hospitals, i.e., at the departments of Cardiology and Internal Medicine of the Leiden University Medical Center, Diaconessenhuis Leiden and Rijnland Hospital Leiderdorp and at the department of Orthopedics of the Leiden University Medical Center, all in the Netherlands. Patients were randomized to a treatment with either phenprocoumon or warfarin and were followed until end of treatment or, when the indication required the treatment to continue over 6 months, follow-up ended at this point. Because warfarin is not registered for use in the Netherlands patients who required ongoing treatment and who were randomized to the warfarin group were switched to a treatment with phenprocoumon.

The second group included in this trial consisted of patients already using acenocoumarol and were recruited at the Leiden Anticoagulation clinic. After written informed consent they were randomized and switched to a treatment with either phenprocoumon or warfarin. Follow-up was again 6 months and like patients of the first group, patients randomized to warfarin switched to phenprocoumon at the conclusion of the trial. If they preferred so, patients of this second group could also choose to switch back to acenocoumarol. Figure 1 summarizes the flow of patients through the study.

All patients participating in the trial were part of the routine care in the Anticoagulation clinic. We obtained approval from Medical Ethics Review Committee of the Leiden University Medical Center before start of the study and all patients gave written informed consent before randomization. The trial is registered in the ISRCTN register with identifier ISRCTN60446748 (http://www.controlled-trials.com).

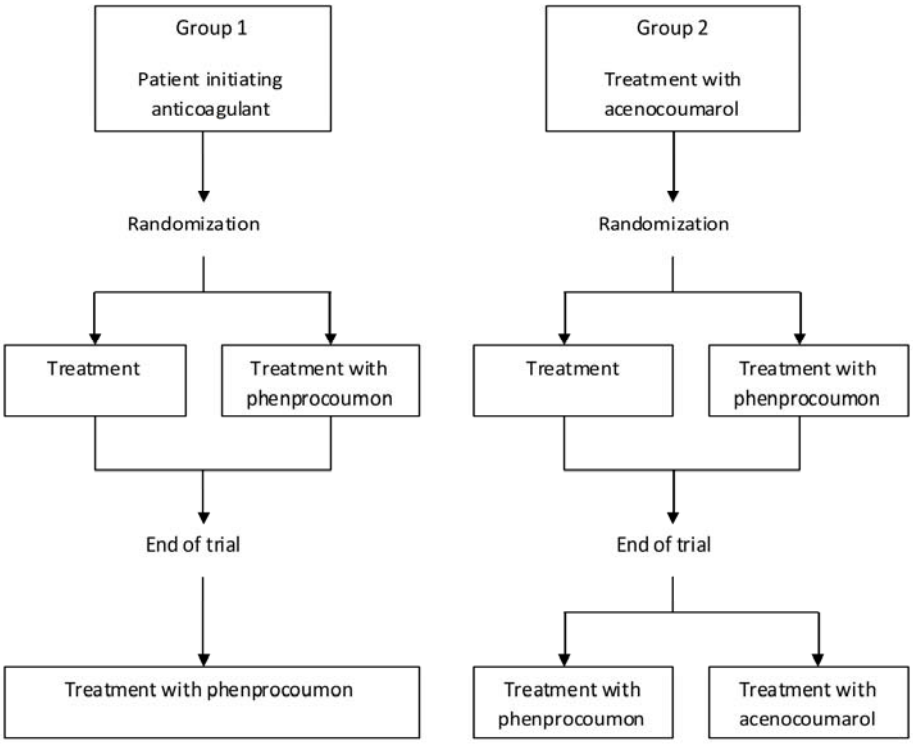

Figure 1. Flowchart of patients in the trial

Analysis

Of the first group of patients, i.e., those who initiated their treatment within the trial, we studied the transition of patients randomized to warfarin who switched to phenprocoumon at end of follow-up. Of the second group of patients, i.e., those already treated with acenocoumarol, we studied the transition from acenocoumarol to phenprocoumon or warfarin at start of follow-up and the transition from warfarin to phenprocoumon at end of follow-up. We did not include the transition from warfarin to acenocoumarol at the end of follow-up because these patients were

already included in the analysis as switchers from acenocoumarol to warfarin when they entered the trial. In a secondary analysis we did look at this transition at the conclusion of the trial separately to investigate whether the transition factor we found was similar to the calculated transition factor at the start of follow-up.

We determined the maintenance dosage by calculating the mean dosage that led to three consecutive INRs within the therapeutic range, with at least 7 days between two INR checks. The maintenance dose was determined over the period closest to the transition date. For the first coumarin used this means the last 3 consecutive INRs in range before switching. After the transition date we considered the first 4 weeks as a wash out period. So, for the second coumarin we searched for the first 3 INRs in range after the wash out period. All determined maintenance dosages were evaluated, and corrected if necessary, by an expert in anticoagulant dosing. Therapeutic ranges were as they are applied in our clinic: INR 2.0-3.5 for indications requiring a low intensity and INR 2.5-4.0 for high intensity.

We performed linear regression analysis. All models were made with starting point at origin. Regression coefficients are given with their 95% confidence intervals. All calculations were performed using the statistical package SPSS version 14.0 (SPSS Inc, Chicago, Ill).

Results

In total 141 transitions were evaluated. Thirty-seven patients initiated their anticoagulant treatment with warfarin and switched to phenprocoumon. Eighty-three patients were already treated with acenocoumarol and of these patients, 39 switched to phenprocoumon and 44 to warfarin. Of these 44 patients randomized to a treatment with warfarin, 21 switched back to phenprocoumon at end of follow-up. General characteristics of all patients are summarized in table 1.

For 13 patients one of the maintenance dosages and for one patient both dosages could not be determined, because they did not have three consecutive INRs in range. The median maintenance dose of phenprocoumon for patients with a target range of 2.0-3.5 (n=68) was 2.09 mg/ day (interquartile range (IQR) 1.50-2.72). For acenocoumarol (n=58) and warfarin (n=81) the maintenance dose was 2.46 mg/ day (IQR 1.79- 3.47) and 4.68 mg/ day (IQR 3.74- 6.60) respectively. Seventy-two patients (51.1%) were stable with their anticoagulant treatment at time of the transition, i.e. the last three INRs were within the therapeutic range. The median interval between the maintenance dose of the first coumarin and the second coumarin was 98 days (IQR 63- 153 days).

Table 1. Patient characteristics

	Warfarin to phenprocoumon N=58	Acenocoumarol to phenprocoumon N= 39	Acenocoumarol to warfarin N=44
Age			
Median (IQR*)	69.5 (63.0 – 77.3)	67.0 (61.0-75.0)	66.0 (61.3-73)
Sex			
Men (%)	43 (74.1)	30 (76.9)	37 (84.1)
Intensity of OAC			
Low (2.0-3.5) (%)	51 (87.9)	26 (66.7)	33 (75.0)
High (2.5-4.0) (%)	7 (12.1)	13 (33.3)	11 (25.0)
Indication for OAC			
Atrial fibrillation	45 (77.6)	20 (51.3)	22 (50.0)
Venous thrombosis	5 (8.6)	2 (5.1)	6 (13.6)
Cardiac other	3 (5.2)	7 (17.9)	8 (18.2)
Peripheral arterial	4 (6.9)	7 (17.9)	6 (13.6)
Other	1 (1.7)	3 (7.7)	2 (4.5)

*IQR=Interquartile range

Transition from warfarin to phenprocoumon

The first mean daily dose of phenprocoumon was 0.48 (95%CI 0.46-0.51) times the last mean daily dosage of warfarin. A loading dosage was given on the first day to 89.4% of the patients, and this loading dosage was approximately 1.6 times the mean daily dosage. 83.0% of patients received a loading dosage on the second day after transition and this was 2.3 times the mean daily dosage. A loading dose of 2.3 times the mean daily dosage was given to 63.8% of patients on the third day after

transition. Few patients (27.7%) received a loading dosage on the fourth day after transition and this was 2.1 times the mean daily dosage. In the wash out period of 4 weeks after transition the median percentage time in the therapeutic range was 62.8% (IQR 37.6 – 96.1).

The transition factor between the maintenance dosage of phenprocoumon and warfarin in milligram was 0.41 (95% CI 0.39 – 0.43), indicating that the maintenance dosage of phenprocoumon is 0.41 times the maintenance dosage of warfarin (figure 2).

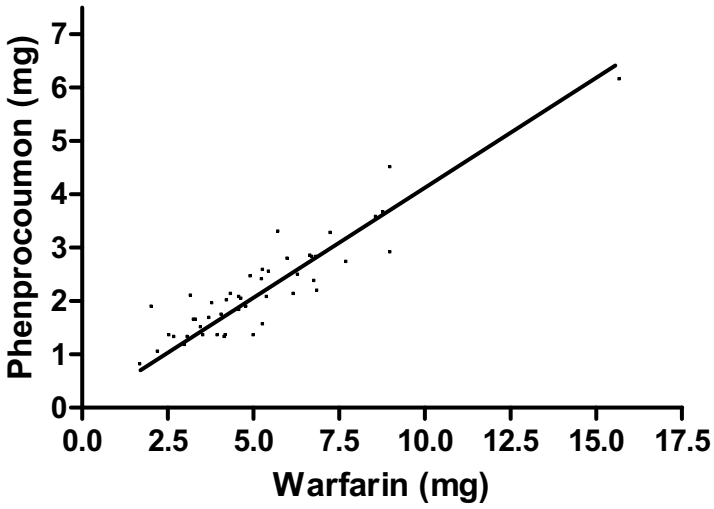

Figure 2. Relation between the maintenance dose of phenprocoumon and warfarin.

Transition from acenocoumarol to phenprocoumon

The first mean daily dose of phenprocoumon was 0.90 (95%CI 0.87-0.94) times the last mean daily dosage of acenocoumarol. A mean loading dosage of 2.5 times the mean daily dosage was given on the first day to 86.8% of the patients. On the

second day 81.6% of the patients received a mean loading dosage of 3.3 times the mean daily dosage, and 63.2% of the patients was prescribed a mean loading dose of 2.5 times the mean daily dosage on the third day after transition. A small fraction of patients (5.3%) received a loading dosage on the fourth day after transition of approximately 2.0 times the mean daily dosage. The median percentage of time in the therapeutic range in the first four weeks was 69.5% (IQR 49.9 – 94.7).

The transition factor between acenocoumarol and phenprocoumon in milligram was 0.84 (95% CI 0.79 – 0.89), meaning that the maintenance dosage of phenprocoumon is 0.84 times the maintenance dosage of acenocoumarol (figure 3).

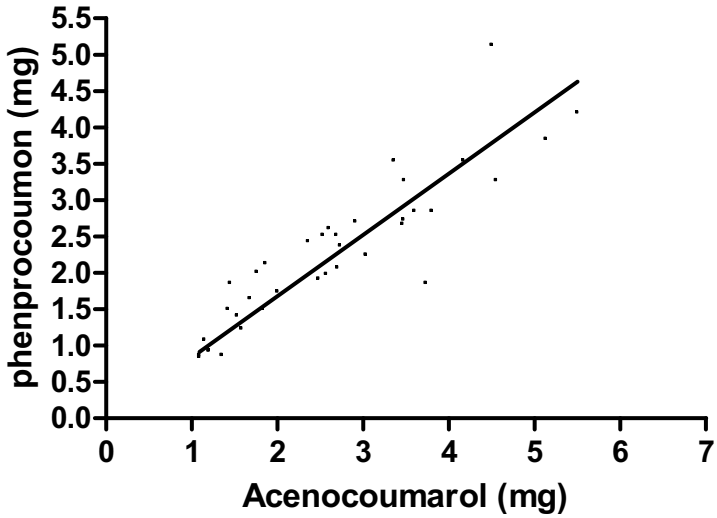

Figure 3. Relation between maintenance dosage of acenocoumarol and phenprocoumon

Transition from acenocoumarol to warfarin

The first mean daily dose of warfarin was 1.59 (95%CI 1.53-1.65) times the last mean daily dosage of acenocoumarol. A loading dosage was given on the first day to 82.9% of the patients, and this loading dosage was on average 1.8 times the

mean daily dosage. 73.2% of the patients also received a loading dosage on the second day after transition and this was 1.8 times the mean daily dosage. A loading dose of 1.6 times the mean daily dosage was given to 36.6% of the patients on the third day after transition. Only one patient received a loading dosage on the fourth day after transition and this was 1.9 times the mean daily dosage. This led to a median percentage of time in therapeutic range in the first four weeks of 66.3% (IQR 48.4 – 95.8).

The transition factor between the maintenance dosage of acenocoumarol and warfarin in milligram was 1.85 (95% CI 1.78 – 1.92), indicating that the maintenance dosage of warfarin is 1.85 times the maintenance dosage of acenocoumarol (figure 4).

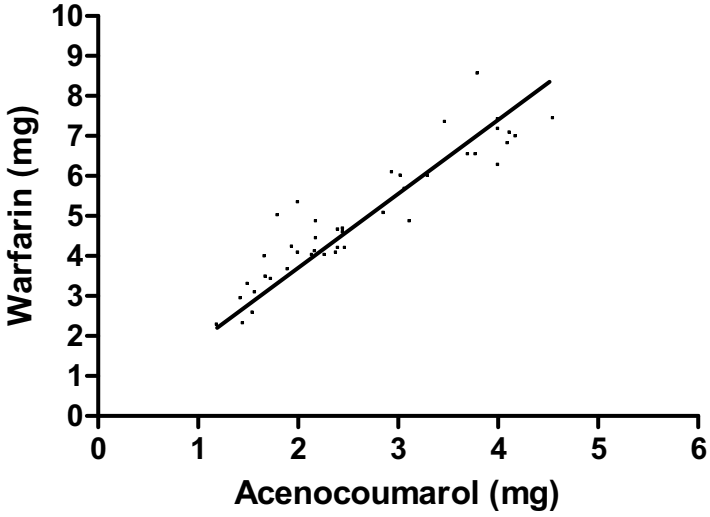

Figure 4. Relation between maintenance dosage of acenocoumarol and warfarin

All transition factors are listed in table 2. Age had minor effects on the transition factors.

Table 2. Transition factors with corresponding 95% confidence intervals

Direction of switch	Transition factor	95% CI
Warfarin to phenprocoumon	0.41	0.39 - 0.43
Phenprocoumon to warfarin	2.36	2.24 - 2.48
Acenocoumarol to phenprocoumon	0.84	0.79 – 0.89
Phenprocoumon to acenocoumarol	1.15	1.08 – 1.22
Acenocoumarol to warfarin	1.85	1.78 – 1.92
Warfarin to acenocoumarol	0.53	0.51 – 0.55

In table 3 the transition factors for different age categories are shown. The transition factors did not differ if we calculated them separately for the two different therapeutic ranges. There were minor differences in the transition factors for stable versus unstable anticoagulated patients which were not clinically relevant.

Table 3. Transition factors with corresponding 95% confidence intervals for different age categories

Direction of switch	Agegroup	N	Transition factor	95%CI
Warfarin to phenprocoumon	<66.7	21	0.40	0.37-0.42
	66.7-74.3	21	0.42	0.38-0.37
	>74.3	16	0.43	0.39-0.48
	Total	58	0.41	0.39-0.43
Acenocoumarol to phenprocoumon	<66.7	17	0.83	0.74-0.93
	66.7-74.3	12	0.83	0.76-0.90
	>74.3	10	0.90	0.83-0.97
	Total	39	0.84	0.79-0.89
Acenocoumarol to warfarin	<66.7	24	1.86	1.74-1.98
	66.7- 74.3	13	1.84	1.73-1.94
	>74.3	7	1.83	1.71-1.96
	Total	44	1.85	1.78-1.92

Of the patients who switched from acenocoumarol to warfarin 21 patients switched back to acenocoumarol at the conclusion of the trial. The transition factor between warfarin and acenocoumarol in these patients in milligram was 0.53 (95%CI 0.50 – 0.56), which is approximately the same as the inverse of the

transition factor we found in patients switching from acenocoumarol to warfarin at start of the trial (1/ 1.85 = 0.54).

Discussion

We investigated the transition factors between the maintenance dosages of the three frequently used coumarins for oral anticoagulant treatment. The maintenance dose of warfarin was 0.41 (95%CI 0.39- 0.43) times the maintenance dose of phenprocoumon. The transition factor between acenocoumarol and phenprocoumon was 0.84 (95%CI 0.79- 0.89) and between acenocoumarol and warfarin 1.85 (95%CI 1.78- 1.92).

Because we had the unique situation of patients switching between warfarin, phenprocoumon and acenocoumarol within a randomized trial, i.e., without a medical reason to switch, we could study the relationship between the maintenance dosages of these three coumarins without bias. Also when we calculate the transition factor between phenprocoumon and warfarin by using the transition factors between acenocoumarol and phenprocoumon and acenocoumarol we find approximately the same result we observed in our patients (0.84/ 1.85 = 0.45 versus 0.41). It should be noted that we investigated the relationship between the maintenance dosages; a transition scheme may also require a loading dose. We gave a description of our management during transition, but we did not investigate whether or not this was the most appropriate way to switch between coumarins.

In some patients the time between the two maintenance doses was very long and we may question whether the dosages were still related to each other since the coumarin sensitivity may vary over time within a patient. However, since these variations are relatively small and random in their direction it is unlikely that this affected our results. This is also supported by the results of our secondary analysis where we found that in patients who switched from acenocoumarol to warfarin and

back to acenocoumarol again the transition factor between acenocoumarol and warfarin is the same as the inverse of the transition factor between warfarin and acenocoumarol.

In our study we found similar results as was found in the study of Kristiansen *et al.* [20]. They reported a transition factor of 2.3 for switching from phenprocoumon to warfarin, where we found a transition factor of 2.4. No literature is known about switching from acenocoumarol to phenprocoumon or from acenocoumarol to warfarin. Several studies showed that the variant alleles CYP2C9*2 or CYP2C9*3 are associated with an increased response to acenocoumarol and warfarin, whereas such an association is unclear for phenprocoumon [10, 21, 22]. These variant alleles could also interfere with the transition factors we presented in this manuscript. Unfortunately it was not possible to investigate this possible effect in our study population since the data were not available. We found minor differences in the transition factors for the different age categories which are not of clinical importance to our opinion.

We calculated the transition factors between the maintenance dosages of the three most frequently used coumarins for oral anticoagulant treatment. With these transition factors physicians can easily determine the maintenance dosage when it is necessary for a patient to switch from one coumarin to another.

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