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REGULAR ARTICLE

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 the end of follow-up. We analysed the switch from acenocoumarol to warfarin or phenprocoumon at the 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: Fifty-eight 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.

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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 h, followed by warfarin with 36–42 h and the longest half-life is seen in phenprocoumon with approximately 140 h [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 outpatient 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 Medicin 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. Fig. 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 (www.controlled-trials.com).

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