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Rombouts, E.K.; Rosendaal, F.R.; Meer, F.J.M. van der

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The effect of vitamin K supplementation on anticoagulant treatment

E. K. ROMBOUTS,* F. R. ROSENDAAL*† and F. J. M. VAN DER MEER*
*Department of Hematology, Leiden University Medical Center, the Netherlands; and †Department of Clinical Epidemiology, Leiden University Medical Center, the Netherlands

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Until recently, the view that dietary vitamin K interferes with oral anticoagulant therapy was based on case reports and a few small experimental studies with extremely high vitamin K intake. In two recent studies the effect of dietary vitamin K on oral anticoagulation was systematically investigated [1,2]. These studies showed that, even in patients on an average diet, changes in vitamin K intake affect anticoagulation. When patients decreased their vitamin K intake the International Normalized Ratio (INR) response was more pronounced than when vitamin K intake was increased [2]. Because changes are proportionally larger in people with a low average vitamin K intake, it is likely that the INR is more sensitive to a varying vitamin K intake in those individuals. Sconce et al. established that daily intake of vitamin K was indeed lower in patients with unstable anticoagulation than in stably anticoagulated patients [3]. Daily supplementation of low doses of vitamin K might thus be beneficial.

To safely start vitamin K supplementation in patients receiving oral anticoagulants, it is important to know the effect of low doses of vitamin K on the INR and on the dose of the anticoagulant drug. The dose–response relationship of vitamin K supplementation on the INR in healthy subjects who received a fixed dose of oral anticoagulants was established by Schurgers et al. [4]. They concluded that 100 μg of vitamin K daily did not significantly interfere with oral anticoagulant therapy. Consequently, Oldenburg suggested 100 μg vitamin K as a recommended supplementation dose in his editorial [5]. However, Kurnik et al. found that, in patients with a low vitamin K status, even daily supplementation doses as low as 25 μg led to an important reduction of the INR [6].

We performed a pilot study to determine the effect of escalating daily doses of vitamin K on the required dose of the anticoagulant drug phenprocoumon. We included patients from the Leiden Anticoagulation Clinic who took part in a program for self-management of anticoagulant treatment. The total study period was 9 weeks, in which the INR was measured at least 3 times a week with a CoaguCheck S coagulometer (Roche Diagnostics, Almere, Netherlands). Patients received vitamin K for 3 weeks. The first and last 3 weeks served as control periods. Five patients received 50 μg and 10 patients 100 μg of oral-based vitamin K1 (250 μg g⁻¹). The primary endpoint was the percentage change in phenprocoumon dose during and after vitamin K needed to keep the INR within therapeutic limits.

Supplementation of 50 μg vitamin K had little effect on the INR and therefore only slight dose-adjustments were made (mean dose increase after starting vitamin K 3% [CI95%: −4% to 10%]). Supplementation of 100 μg resulted in a mean dose increase of 9% (CI95%: 0–19%, Fig. 1). There was considerable inter-individual variability in response with dose adjustments ranging from −7% to 37%. In the three weeks of follow-up after the vitamin K was discontinued phenprocoumon doses were lowered to pre-substitution values (mean change of −7%, CI95%: −15% to 0%).

Our results show that daily supplementation up to 100 μg can be given without a relevant decrease in the INR, on the condition of frequent monitoring during and after the supplementation to allow timely dose adjustments.
References


Influence of endotoxin challenge on protein S and C4b-binding protein in healthy subjects

K. S. KRABBE,*† H. BRUUNSGAARD,*† A. HILLARP‡, and S. THORSEN§

*Centre of Inflammation and Metabolism, Department of Infectious Diseases, Rigshospitalet, Copenhagen, Denmark; †Copenhagen Muscle Research Centre, Rigshospitalet, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark; ‡Department of Clinical Chemistry, Lund University, University Hospital, Malmo, Sweden; and §Department of Clinical Biochemistry, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark


The acute phase response (APR) is a systemic response to local inflammatory processes elicited by infection and/or other types of tissue injury [1,2]. It serves to limit the effect of damaging agents by inducing a largely cytokine-mediated series of systemic events, such as fever, altered metabolism, changes in concentrations of a series of blood proteins (acute phase proteins), and changes in vascular permeability and hematologic parameters. Mainly tumor necrosis factor (TNF)-z, interleukin (IL)-6 and IL-1 induce the changes in synthesis of acute phase proteins. Intravenous injection of endotoxin provides a highly controlled model to investigate the APR [3]. Studies of patients with sepsis and of in vivo endotoxin challenge of healthy subjects have shown that the APR promotes thrombin generation as reflected by an increased formation of thrombin–antithrombin complex and prothrombin fragment 1 + 2 [4–6]. Levels of the anticoagulant proteins; tissue factor pathway inhibitor, protein C and antithrombin are often decreased in patients exhibiting an APR, mainly because of increased consumption of these three proteins [4,5]. In the model of human endotoxemia the levels of antithrombin and tissue factor pathway inhibitor are not or only slightly affected, whereas protein C levels decrease about 15% partly or wholly as a result of thrombin-catalyzed conversion of protein C to activated protein C [5,7]. The anticoagulant protein, protein S is an essential cofactor to activated protein C in the inactivation of factors Va and VIIIa [8]. Effective enhancement of activated protein C-mediated inactivation of factor VIIIa by protein S requires the presence of FV. About 60% of protein S forms an