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The effect of vitamin K supplementation on anticoagulant treatment

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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 sug-

gested 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 supplement 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 oil-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% [95% confidence interval (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.

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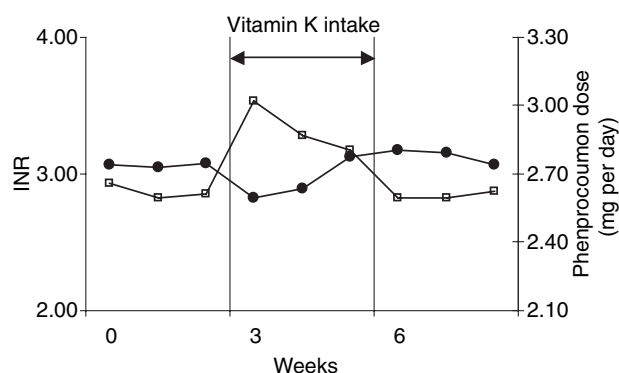


Fig. 1. Effect of vitamin K substitution on the mean International Normalized Ratio (INR) (●) and the mean phenprocoumon dose (□) in 10 patients receiving 100 µg vitamin K daily.

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

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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)- α , 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

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