5 Blinder D, Manor Y, Martinowitz U, Taicher S. Dental extractions in patients maintained on oral anticoagulant therapy: comparison of INR value with occurrence of postoperative bleeding. *Int J Oral Maxillofac Surg* 2001; **30**: 518–21.
6 Evans IL, Sayers MS, Gibbons AJ, Price G, Snooks H, Sugar AW. Can warfarin be continued during dental extraction? Results of a randomized controlled trial. *Br J Oral Maxillofac Surg* 2002; **40**: 248–52.
7 Devani P, Lavery KM, Howell CJ. Dental extractions in patients on warfarin: is alteration of anticoagulant regime necessary? *Br J Oral Maxillofac Surg* 1998; **36**: 107–11.
8 Wahl MJ. Myths of dental surgery in patients receiving anticoagulant therapy. *J Am Dent Assoc* 2000; **131**: 77–81.

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*

To cite this article: Rombouts EK, Rosendaal FR, van der Meer FJM. The effect of vitamin K supplementation on anticoagulant treatment. *J Thromb Haemost* 2006; **4**: 691–2.

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 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.

Correspondence: F. J. M. van der Meer, Leiden University Medical Center, Department of Hematology, PO Box 9600, 2300 RC Leiden, The Netherlands.
Tel.: +31 71 526 2267; fax: +31 71 526 6755; e-mail: f.j.m.van_der_meer@lumc.nl

Received 11 November 2005, accepted 28 November 2005

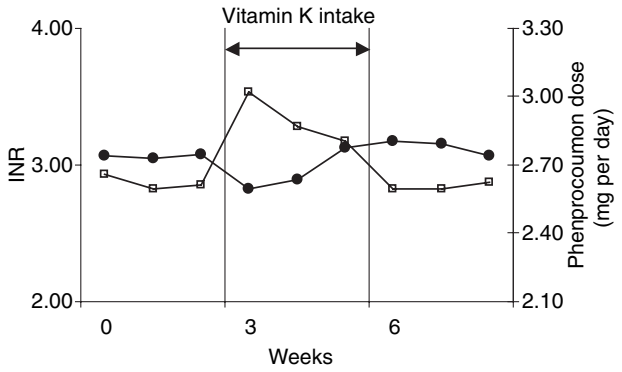

Fig. 1. Effect of vitamin K substitution on the mean International Normalized Ratio (INR) (●) and the mean phenprocoumon dose (□) in 10 patients receiving 100 μg vitamin K daily.

References

1 Khan T, Wynne H, Wood P, Torrance A, Hankey C, Avery P, Kesteven P, Kamali F. Dietary vitamin K influences intra-individual variability in anticoagulant response to warfarin. *Br J Haematol* 2004; **124**: 348–54.

2 Franco V, Polanczyk CA, Clausell N, Rohde LE. Role of dietary vitamin K intake in chronic oral anticoagulation: prospective evidence from observational and randomized protocols. *Am J Med* 2004; **116**: 651–6.

3 Sconce E, Khan T, Mason J, Noble F, Wynne H, Kamali F. Patients with unstable control have a poorer dietary intake of vitamin K compared to patients with stable control of anticoagulation. *Thromb Haemost* 2005; **93**: 872–5.

4 Schurgers LJ, Shearer MJ, Hamulyak K, Stocklin E, Vermeer C. Effect of vitamin K intake on the stability of oral anticoagulant treatment: dose-response relationships in healthy subjects. *Blood* 2004; **104**: 2682–9.

5 Oldenburg J. Vitamin K intake and stability of oral anticoagulant treatment. *Thromb Haemost* 2005; **93**: 799–800.

6 Kurnik D, Loebstein R, Rabinovitz H, Austerweil N, Halkin H, Almog S. Over-the-counter vitamin K(1)-containing multivitamin supplements disrupt warfarin anticoagulation in vitamin K(1)-depleted patients. *Thromb Haemost* 2004; **92**: 1018–24.

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*

To cite this article: Krabbe KS, Bruunsgaard H, Hillarp A, Thorsen S. Influence of endotoxin challenge on protein S and C4b-binding protein in healthy subjects. *J Thromb Haemost* 2006; **4**: 692–4.

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

Correspondence: Karen Suárez Krabbe, Centre of Inflammation and Metabolism, Department of Infectious Diseases, 7641 Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
E-mail: karen.krabbe@dadlnet.dk

Received 4 October 2005, accepted 8 November 2005