

blood

2007 109: 3607-3608
doi:10.1182/blood-2006-12-063271

Response: vitamin K supplementation during oral anticoagulation: no real cause for concern

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Correspondence

To the editor:

Vitamin K supplementation during oral anticoagulation: cautions

In response to the paper by Sconce et al,¹ we would like to point out that we have previously suggested the possibility of using vitamin K as a buffer to increase the stability of oral anticoagulation therapy.² However, we suggested the use of vitamin K₂ instead of vitamin K₁. The potential danger of giving K₁ with warfarin is that it may increase the arterial calcification risk. There are several indications that the use of K₂ may have at least the same ability to stabilize oral anticoagulation and appears to prevent arterial calcification. The drawbacks of using K₁ as a buffer to stabilize the anticoagulation response include the following: (1) K₁ has a relatively short half-life (1-2 hours), so that a single daily dose may result in substantial fluctuations of circulating and tissue K₁ concentrations. Therefore, the stability of anticoagulation may be further improved by using a vitamin K species with a longer half-life. (2) K₁ is taken up preferentially by the liver³ so that extrahepatic tissues are more susceptible to vitamin K deficiency than the liver. This effect is exacerbated when K₁ and warfarin are combined; indeed, this combination has been used by Price et al to induce rapid arterial calcification.⁴ Although the amount of warfarin used by Price et al to induce calcification in rats is higher than would normally be used in oral anticoagulation therapy, there are reports that patients on long-time normal warfarin therapy have increased calcification of aortic valves.^{5,6} Therefore, though increasing both K₁ intake and warfarin dosage may improve oral anticoagulation stability, it probably also increases vascular calcification risk.^{5,6}

A major advantage of K₂ is that it is not preferentially targeted to the liver. A number of tissues—including the vessel wall—accumulate K₂ at high levels.⁶ This results in protection by K₂ but not by K₁ against warfarin-induced calcification.⁷ Also, K₂ can be used in the liver equally as well as K₁. Of the commercially available forms, we recommend MK-7 (NattoPharma, Oslo, Norway; or E. T. Horn, La Mirada, CA). MK-7 is transported to extrahepatic tissues via low-density lipoprotein (LDL).⁸ A further advantage of MK-7 is that it has a relatively long half-life (3 days). This longer half-life will probably result in more stable anticoagulation.

Although vitamin K₂ may have signaling functions independent from its role in gamma glutamyl carboxylation, supplementation with vitamin K₂ (MK-7) in doses as high as 45 mg/day seems to have no adverse effects.⁹ Indeed, it seems to impede the growth of

certain tumors and also to promote vascular health,⁹ and reduces fractures in postmenopausal women.¹⁰

Based on these considerations, we propose that a new trial be designed in which patients on anticoagulation therapy receive MK-7 rather than K₁. At first it will be necessary to adjust the International Normalized Ratio (INR) based upon the dose of MK-7 and warfarin. These patients should also be followed to determine the extent to which this protocol prevents arterial calcification. In this regard, it is noteworthy that the risk of cardiovascular calcification by oral anticoagulation therapy (even without additional K₁) is receiving increasing attention.^{5,6}

Darrel W. Stafford, Harold R. Roberts, and Cees Vermeer

Conflict-of-interest disclosure: D.W.S. has applied for patents on VKOR and its use in predicting warfarin dosage. C.V. is a consultant for E. T. Horn and does contract research for NattoPharma.

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Response:

Vitamin K supplementation during oral anticoagulation: no real cause for concern

We are familiar with the concept that oral anticoagulants, by inhibiting the recycling of vitamin K epoxide into its quinone form, might interfere with the functioning of glutamate-containing proteins not associated with hemostasis, in particular matrix Gla-protein, the potent inhibitor of soft tissue calcification, and osteocalcin, promoter of bone formation. The use of coumarins has increased rapidly in the last 15 years following the first publication

that anticoagulation therapy is beneficial for thromboembolic prophylaxis in patients with atrial fibrillation.¹ Long-term use of coumarins, in what are now large patient populations, has not firmly established a clinically significant association between therapy and risk of arterial calcification. Work in young rats has established that menaquinone (vitamin K₂), but not phylloquinone (vitamin K₁), has a protective effect against warfarin-induced

arterial calcification, perhaps due to the preferential absorption of vitamin K₂ by arterial vessel walls or its more efficient use by carboxylase enzymes.² However, warfarin doses used in the rat model greatly exceed those received by human subjects on long-term anticoagulant therapy. We hold the view that the potential benefits, in terms of reducing bleeding risk (the consistently reported main adverse effect of oral anticoagulants), which we noted in response to supplementation with vitamin K₁,³ outweigh the hypothetical risk of vascular calcification associated with the incremental rise (16% in our study) in warfarin dose.

While the absence of reports of long-term adverse effects in terms of clinically relevant harm from cardiovascular calcification in anticoagulated patients is reassuring, indirect evidence such as that menaquinone is inversely associated with severe aortic calcification as measured by lumbar spine x-ray in asymptomatic individuals,⁴ and the reported association between aortic valve calcification and oral anticoagulant (OA) therapy⁵ (although explainable as a marker of diseases for which treatment with OACs was commenced rather than a response to warfarin), merits further study. Any such investigation, however, will require a robustly designed trial (in terms of power and randomization and with relevant clinical outcomes in terms of coronary artery events, for example) to test the hypothesis that vitamin K₂, through its longer half-life and greater arterial accumulation, has a greater benefit-risk ratio compared with K₁.

The theoretical concerns, while worthy of exploration, should not discourage use of vitamin K₁, in the meantime, to improve

safety of anticoagulation in the unstable patient, or discourage further exploration of its role in anticoagulation population in general, where intraindividual variability in response makes regular anticoagulation monitoring a necessity.

Elizabeth Sconce, Hilary Wynne, and Farhad Kamali

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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To the editor:

Acute thrombocytopenia caused by sensitivity to the glucuronide conjugate of acetaminophen

Several years ago, we described in *Blood* a group of patients who presented with acute, severe thrombocytopenia after taking acetaminophen (Tylenol; McNeil Consumer Healthcare, Guelph, ON, Canada) or naproxen (Aleve; Bayer Health Care, Morris-town, NJ) and showed that in each case a platelet-reactive antibody dependent on a drug metabolite (acetaminophen sulfate or naproxen glucuronide) was the apparent cause of platelet destruction.¹ We wish to describe here a patient who experienced repeated episodes of acute thrombocytopenia after taking acetaminophen who was sensitized to a different metabolite of acetaminophen: acetaminophen glucuronide.

A 4-year-old girl presented with florid petechial hemorrhages and a platelet count of $12 \times 10^9/L$ ($12\,000/\mu L$). Other hematologic indices were normal. Platelets returned to normal in 1 week. Four months later, she presented with fever, extensive petechiae and ecchymoses, and bleeding from the buccal mucosa. Her platelet count was $15 \times 10^9/L$ ($15\,000/\mu L$). In the belief she might have recurrent idiopathic thrombocytopenia (ITP), she was given prednisone. Platelets returned to normal in 4 days. Two months later, she had a third, virtually identical presentation. At this time, a possible connection between the thrombocytopenic episodes and ingestion of acetaminophen was suspected. Because it was felt to be medically important that the cause of the thrombocytopenic episodes be established and with the consent of parents, she was challenged 2 weeks later with a single 200-mg dose of acetaminophen. A few hours later, she developed a fever of 39°C. On the next morning, petechiae and ecchymoses were present, and the platelet count had dropped from $209 \times 10^9/L$ ($209\,000/\mu L$) to $17 \times 10^9/L$ ($17\,000/\mu L$). Platelets returned to normal in 4 days on prednisone.

With avoidance of acetaminophen, she had no further episodes of thrombocytopenia over 18 months.

Using a flow cytometric assay,¹ platelet-reactive antibodies specific for acetaminophen or acetaminophen sulfate could not be found in a blood sample taken 2 months after the fourth thrombocytopenic episode. However, an IgG antibody was identified that reacted strongly with platelets in the presence of acetaminophen glucuronide (Sigma-Aldrich, St Louis, MO; Figure 1) at dilutions

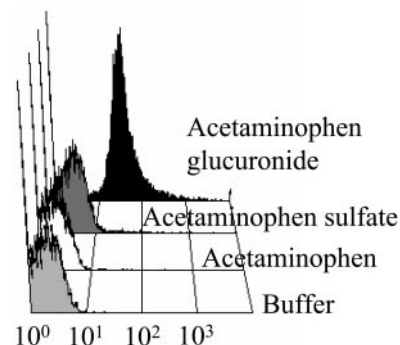


Figure 1. The patient's antibody (1:5 dilution) reacted with normal platelets in the presence of acetaminophen glucuronide, but not acetaminophen or acetaminophen sulfate. Washed platelets (5×10^6) were combined with patient serum in the presence or absence of 0.4 mM acetaminophen or the metabolite indicated in a final volume of 50 μL . After incubation for 1 hour, the platelets were washed in the presence or absence of the indicated drug or metabolite (0.2 mM). Bound human IgG was detected by the addition of FITC goat (Fab')₂ anti-human IgG (H+L) (1:200; Jackson ImmunoResearch, West Grove, PA). No reaction occurred with normal serum under same conditions. Abscissa indicates mean platelet fluorescence intensity in arbitrary units.