Adverse Effects of Coumarin Anticoagulants

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Summary

The biochemistry of vitamin K metabolism and the role of vitamin K-dependent γ-carboxylation of the vitamin K-dependent coagulation factors are now well understood. Likewise, there is a clear understanding of the role of oral anticoagulants in the inhibition of these coagulation factors. However, the effect of oral anticoagulants on extrahepatic γ-carboxylated proteins such as osteocalcin and matrix γ-carboxyglutamate (Gla)-protein (MGP), and the effects of long term anticoagulants on bone mineral metabolism are just now being recognised. The relevance of these observations on mineral metabolism for elderly individuals, and in particular postmenopausal women who are on long term anticoagulants, is still unknown but worthy of continued close observation.

The most significant hazard of oral anticoagulants is haemorrhage. Clinical trials continue to demonstrate that less intense (lower dosage) warfarin therapy can significantly decrease this risk of haemorrhage while at the same time providing equal efficacy when compared to more intense warfarin therapy. The more widespread use of the International Normalised Ratio (INR) for the control of anticoagulants will undoubtedly further decrease the risk of haemorrhage, but new innovations such as the use of ultra low-dose warfarin or newer techniques for the continued monitoring of oral anticoagulants are still required, particularly as the indications for oral anticoagulants continue to expand.
The oral anticoagulants are the most commonly used agents in the long term prophylaxis and treatment of both arterial and venous thromboembolic events. As new and expanded indications for their use are developed, such as the prevention of recurrent myocardial infarction or systemic embolism in atrial fibrillation, the use of oral anticoagulants continues to rise in a fashion similar to that of a newly discovered agent. Many patients receiving these drugs are in the older age group and are, therefore, at greater risk of some of the adverse effects of these drugs. In this article we will review the metabolism of vitamin K and the interference by the oral anticoagulants in the production of γ-carboxyglutamate (Gla) in the liver and the bones as well as the other adverse effects of these agents.

1. The Vitamin K Cycle and Vitamin K Deficiency

Vitamin K is responsible for the post-translational conversion of glutamate residues into Gla in a limited number of proteins, the best known of which are the blood coagulation factors II, VII, IX, X, protein C and protein S, and bone matrix proteins. The best known bone matrix proteins are osteocalcin and matrix Gla-protein (MGP) [Vermeer 1990].

γ-Carboxyglutamic acid permits the binding of calcium by these proteins, and in the presence of calcium the coagulation factors undergo a conformational change that is required for their binding to various active cofactors on cell surfaces (Furie & Furie 1990). The reduced form of vitamin K (KH₂) acts as a coenzyme for carboxylase. The oxidation of vitamin KH₂ by oxygen into vitamin K epoxide (KO) provides energy to fix carbon dioxide (CO₂) at the γ-position of a glutamate residue (fig. 1). The vitamin KO is then recycled, first by vitamin K epoxide reductase to vitamin K (quinone) and then by vitamin K reductase to vitamin KH₂ (hydroquinone). It is essential that each molecule of vitamin K is recycled several hundred times before being metabolised.

The oral anticoagulants inhibit vitamin KO reductase and possibly vitamin K reductase, thereby depleting vitamin KH₂ and causing the build-up of vitamin KO in the tissues such as the liver and plasma (fig. 1).

The most important forms of vitamin K are phylloquinones (vitamin K₁) and menaquinones (vitamin K₂) [Vermeer 1990].

Phylloquinones are found in green, leafy vegetables such as spinach, cabbage and broccoli. Deficiencies of these vegetables in the diet can cause vitamin K deficiency, whereas excessive amounts can reverse the effects of oral anticoagulants. The menaquinones occur in various foods such as yoghurt and organ meats. They are also produced by the bacterial flora of the colon and possibly the small intestine. Factors interfering with the production or absorption of these menaquinones, e.g. broad-spectrum antibiotics, may lead to vitamin K deficiency (Pineo et al. 1973) and interference with anticoagulant control. Also, certain cephalosporins containing an N-methyl-thiotetrazole side chain may interfere directly with vitamin KO reductase in the liver (Lipsky 1988) thereby leading to vitamin K deficiency. Most of the vitamin K stores in the liver are menaquinones and it is thought that most of these originate from the diet rather than the intestinal flora (Vermeer 1990).

Large doses of vitamin K can overcome the blockade of vitamin KH₂ by oral anticoagulants presumably because vitamin K reductase is less sensitive to the coumarins than is vitamin KO reductase (Vermeer 1990) [fig. 1]. This reversal of oral anticoagulants applies to the first generation agents such as warfarin, but does not apply to the second generation rodenticides known as the 'super warfarins' which have an extremely long half-life. Accidental consumption of these agents requires repeated injections of vitamin K and fresh frozen plasma for up to 1 or 2 years to completely overcome their effects (Exner et al. 1992; Lipton & Klass 1984).

2. Monitoring of Oral Anticoagulant Therapy

Normally, there is a direct correlation between the dose of warfarin and the anticoagulant effect.