Vitamin K oral anticoagulant

Inhibition of the synthesis or activity of Factor X is the mechanism of action for many anticoagulants. Warfarin, a synthetic derivative of coumarin, is the most widely used oral anticoagulant in the US. In some European countries, other coumarin derivatives (phenprocoumon and acenocoumarol) are used. These agents are vitamin K antagonists (VKA). Vitamin K is essential for the hepatic synthesis of Factors II (prothrombin), VII, IX and X.

Despite the application of many parenteral (unfractionated heparin and Low-molecular-weight heparins) and oral anticoagulant vitamin K antagonist (VKA) drugs, the prevention and treatment of venous and arterial thrombosis remain major medical challenges.

Vitamin K oral anticoagulant drugs are 4-hydroxycoumarin derivatives, which exert their anticoagulant effect by inhibiting vitamin K epoxide reductase and, possibly, vitamin KH2 reductase [1].

These compounds act by reducing vitamin KH2 (reduced form of vitamin K) levels, thereby limiting the cofactor effect of vitamin K on the γ-carboxylation of the vitamin K-dependent coagulation factors II, VII, IX, and X. VKAs also limit the effect of anticoagulant proteins, protein C and protein S, resulting in an inhibition of these proteins [2] [3].

During the last 60 years, vitamin K antagonists (VKAs), which include coumarin derivatives (eg, warfarin and acenocoumarol), have been the only oral anticoagulants used [4].

The VKA dose is determined on an individual basis (not fixed), whereas novel non vitamin K oral anticoagulant are administered in fixed doses, except when a patient has a functional disorder of the liver or kidney.

The evolution of vitamin K, from a dietary deficiency in birds to a postribosomal modifier of prothrombin in man, has been a fascinating scientific saga. Its antivitamin, the oral anticoagulant drugs, has been a powerful probe both of vitamin K action and of drug interactions. These agents have emerged from a limbo of clinical therapeutics to become a light of human pharmacology [5].

Indications

Treatment with VKAs is indicated in various medical situations, such as for the treatment of Deep-Vein Thrombosis (Deep-vein thrombosis) and pulmonary embolism (PE), and the prevention of recurrence, atrial fibrillation (AF) and stroke in patients with NVAF, acute myocardial infarction, and vasculopathy, as well as in patients with tissue heart valves or mechanical prosthetic cardiac valves. These drugs are also used as prophylaxis for VTE in high-risk patients (eg, post-orthopedic surgery, embolic peripheral, and arterial disease) [6] [7].

Complications

Intracranial haemorrhage (ICH) is the most feared complication of oral anticoagulation for patients on vitamin K antagonists (VKAs).

This concerns mostly patients with atrial fibrillation or venous thromboembolism, or those carrying

mechanical heart valves. The incidence of VKA-associated ICH is 0.7% per year with atrial fibrillation [8] and 0.5% per year in the patients with a mechanical heart valve [9].

1)
Ferlund P, Stenflo J, Roepstorff P, Thomsen J. Vitamin K and the biosynthesis of prothrombin. V. Gamma-carboxyglutamic acids, the vitamin K-dependent structures in prothrombin. J Biol Chem. 1975;250(15):6125–6133.
2)
Holy EW, Beer JH. Update on the status of new oral anticoagulants for stroke prevention in patients with atrial fibrillation. Cardiovasc Med. 2013;16:103–114.
3) , 6)
Hirsh J, Dalen JE, Anderson DR, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest. 1998;114:445S–469S.
4)
Gómez-Outes A, Suárez-Gea ML, Calvo-Rojas G, et al. Discovery of anticoagulant drugs: a historical perspective. Curr Drug Discov Technol. 2012;9(2):83–104.
5)
O'Reilly RA. Vitamin K and the oral anticoagulant drugs. Annu Rev Med. 1976;27:245-61. Review. PubMed PMID: 779597.
7)
Ickx BE, Steib A. Perioperative management of patients receiving vitamin K antagonists. Can J Anaesth. 2006;53(6 Suppl):S113–S122.
8)
Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, Pais P, Dans A, Eikelboom J, Oldgren J, Pogue J, Reilly PA, Yang S, Connolly SJ; RE-LY Investigators. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet 2010;376:975–998
9)
Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJ, Vandenbroucke JP, Brie¨t E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. N Engl J Med 1995;333:11–17.