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Review

Effects of warfarin on biological processes other than haemostasis: A review

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ABSTRACT

Warfarin is the world's most widely used anticoagulant drug. Its anticoagulant activity is based on the inhibition of the vitamin K-dependent (VKD) step in the complete synthesis of a number of blood coagulation factors that are required for normal blood coagulation. Warfarin also affects synthesis of VKD proteins not related to haemostasis including those involved in bone growth and vascular calcification. Antithrombotic activity of warfarin is considered responsible for some aspects of its anti-tumour activity of warfarin. Some aspects of activities against tumours seem not to be related to haemostasis and included effects of warfarin on non-haemostatic VKD proteins as well as those not related to VKD proteins. Inflammatory/immunomodulatory effects of warfarin indicate much broader potential of action of this drug both in physiological and pathological processes. This review provides an overview of the published data dealing with the effects of warfarin on biological processes other than haemostasis.

1. Warfarin: general aspects

Warfarin is vitamin K antagonists (VKA) which belongs to the family of coumarins. The utilization of warfarin and its analogues in prophylactic medicine is based on the inhibition of the vitamin K-dependent (VKD) step in the complete synthesis of a number of blood coagulation factors in the liver that are required for normal blood coagulation (Furie, 2000). Warfarin affects interconversion of Vitamin K (VK) and its 2, 3 epoxide by inhibiting vitamin K epoxide reductase (VKOR) which results in depletion of hidroquinone, KH2. The KH2 is cofactor for γ-glutamyl carboxylase (GGCX), a VKD enzyme which is necessary for posttranslational modification (carboxylation) of glutamyl (Gla) residues needed for generation of biologically active coagulation factors. Depletion of γ-glutamyl carboxylase activity results in the accumulation of undercarboxylated inactive intracellular precursors of several VKD proteins involved in the process of coagulation including factor II (prothrombin, PT), factor VII (FVII), factor IX (FIX) and factor X (FX) (Furie, 2000). Impaired production of these essential blood clotting factors influenced by warfarin, results in an increase in clotting time up to the point where no clotting occurs. Warfarin is in use for more than 60 years, and it is still the most widely used anticoagulant drug in the world (Pineo and Hull, 2003; Pirmohamed, 2006). According to estimations there are over 30 million prescriptions of warfarin in USA (Pirmohamed et al., 2015) and over 1% of population in Great Britain use warfarin (Pirmohamed, 2006). Owing to its anticoagulant effect and efficient (complete and fast) absorption in the intestine, warfarin turned out to be the most widely used drug in the prophylaxis and treatment of venous thrombosis, pulmonary as well as systemic embolism (Du et al., 2008; Wang et al., 2009). For majority of indications a moderate anticoagulant effect (i.e. INR 2.0–3.0) was considered appropriate, which is based on clinical trials (Trial, 1998), but for some patients, such as those with mechanical heart valves, a target INR of 2.5–3.5 or higher is required (Salem et al., 2008; Singer et al., 2008). Because of narrow therapeutic index, it is difficult to maintain defined range of anticoagulation in patients and there is a risk of bleeding (due to warfarin overdose) or thrombotic events (at too low warfarin dose) (Boulanger et al., 2006). According to data from Great Britain since 2004, due to adverse effects, warfarin has reached the high third position on the list of drugs which caused the admission to hospital (Pirmohamed et al., 2004). Data from United States showed that warfarin was the main cause of serious adverse effects and hospitalizations in older individuals (Budnitz et al., 2011). Haemorrhage is the

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Abbreviations

AKI	Acute Kidney Injury
ARN	Anticoagulant-Related Nephropathy
BGP	Bone Gla Protein
CKD	Chronic Kidney Disease
cMGP	carboxylated Matrix Gla Protein
CYP	Cytochrome P450
dp-ucMGP	desphospho-uncarboxylated Matrix Gla Protein
GAS6	Growth Arrest-Specific Gene 6
GGCX	γ-Glutamyl Carboxylase
Gla	Glutamyl
IFN-γ	Interferon-γ
IL	Interleukin
INR	International Normalized Ratio
LMWH	Low Molecular Weight Heparins
LPS	Lypopolysaccharide
MDA	Malondialdehyde
MERTK	Tyrosine-Protein Kinase Mer
MGP	Matrix Gla Protein
MLN	Mesenteric Lymph Node
NAC	*N*-Acetyl Cysteine
NK cells	Natural Killer cells
OC	Osteocalcin
OSCC	Oral Squamous Carcinoma Cell
PARs	Proteinase-Activated Receptors
PC	Protein C
PCa	Prostate Cancer
PCNA	Proliferating Cell Nuclear Antigen
PHA	Phytohaemagglutinin
PMN	Polymorphonuclear
PT	Prothrombin
PS	Protein S
PSA	Prostate-Specific Antigen
PZ	Protein Z
RANKL	Receptor Activator of Nuclear Factor-Kappa B Ligand
SCLC	Small Cell Lung Cancer
SNP	Single Nucleotide Polymorphism
SOD	Superoxide Dismutase
TAM	TYRo-3, AXL and MER Receptor Tyrosine Kinases
TG2	Transglutaminase 2
TGFβ1	Transforming Growth Factor Beta1
TMG	Transmembrane Gla Protein
TNF	Tumour Necrosis Factor
ucOC	under-carboxylated Osteocalcin
VK	Vitamin K
VKA	Vitamin K Antagonists
VKD	Vitamin K-Dependent
VKOR	Vitamin K Epoxide Reductase
VSMC	Vascular Smooth Muscle Cells
VTE	Venous Thromboembolism
WISN	Warfarin-Induced Skin Necrosis
WRN	Warfarin-Related Nephropathy

major adverse effect of warfarin therapy. Warfarin-induced bleeding affects variety of tissues and organs (Brodsky et al., 2009, 2011; Suárez-Pinilla et al., 2014) and might lead to clinical complications, often with unknown underlying mechanisms (Bekheit et al., 2014; Linkins et al., 2003). Subtherapeutic INR values often result in thromboembolism (Clark et al., 2008) in patients treated with warfarin, with resulting prescription of bridge therapy with other anticoagulants (Kovacs et al., 2004). There is thus a need for frequent laboratory testing in clinical settings. Besides usual clinical care, another care models (self-testing and/or self-measurements) were considered concerning their potential to improve anticoagulation control (Bloomfield et al., 2011; Garcia-Alamino et al., 2010; Menendez-Jandula et al., 2005). The risk of over- or under -coagulation depends on extrinsic factors (ongoing medication and diet) as well as intrinsic factors (age and polymorphism of p450/

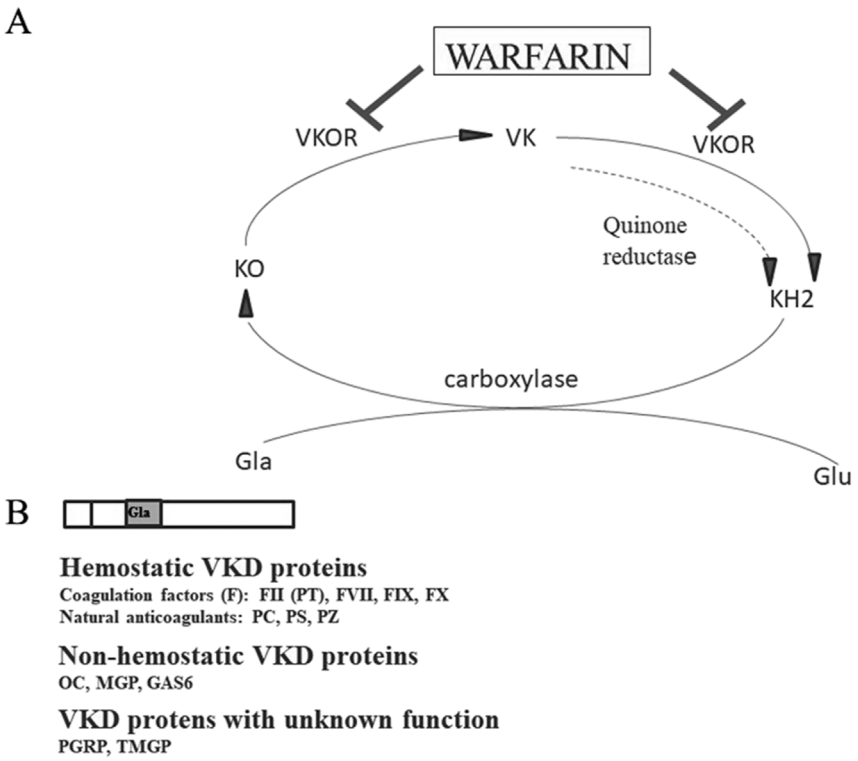

Fig. 1. Warfarin and vitamin K-dependent proteins. A) Carboxylation (conversion of Glu to Gla residues) of vitamin K-dependent proteins (VKD proteins) is linked to vitamin K (VK) cycle. VK cycle enables γ-glutamyl carboxylation and is a pathway of VK recovery from its epoxide (KO) form to the active reduced form (KH2) needed for the γ-glutamyl carboxylation. VK is mainly recycled by VKOR (vitamin K epoxide reductase). Coumarin-based anticoagulants, including warfarin, inhibit VKOR enzymes. NAD(P)H-dependent quinone reductase can also reduce VK. B) Generalized structure of VKD proteins with Gla domain and list of VKD proteins. PC, Protein C; PS, Protein S; PZ, Protein Z; OC, osteocalcin/bone Gla protein; GAS6, coded by Growth arrest gene 6; MGP, matrix Gla protein; PGRP, Proline-Rich Gla Proteins; TMGP, Transmembrane Gla Proteins.