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CHAPTER

WARFARIN

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INTRODUCTION

Vitamin K antagonists (VKAs), including warfarin, have been the core of oral anticoagulation for decades. Warfarin is used for stroke prevention in atrial fibrillation, prevention of valvular thrombosis in biologic and mechanical valve replacement, and prevention and treatment of deep vein thrombosis, pulmonary embolism, and other manifestations of venous and arterial thromboembolism. Due to a narrow therapeutic index, highly variable dose response and the significant impact of diet, disease, and drugs on warfarin pharmacokinetics and pharmacodynamics, it is an agent that requires frequent monitoring and dosage adjustment to maintain its efficacy and safety.

PHARMACOLOGY[1]

Warfarin and other VKAs act by inhibition of the hepatic synthesis of vitamin K dependent clotting factors II, VII, IX, and X. These clotting factors (and the anticoagulant substances protein C and protein S) become biologically active by gamma-carboxylation involving vitamin KH2. In a vitamin K hepatic recycling process that maintains a continuous supply of vitamin KH2 for clotting factor synthesis, vitamin KH2 is oxidized to vitamin KO and subsequently converted to vitamin K by vitamin K epoxide reductase (VKOR) and then back to vitamin KH2 by vitamin K1 reductase. Warfarin inhibits VKOR and vitamin K1 reductase, resulting in accumulation of biologically inactive vitamin KO and a reduction in vitamin K dependent clotting factor synthesis. The full anticoagulant effect of warfarin occurs when previously activated clotting factors are depleted at rates consistent with their biologic half-lives, typically within 5–10 days (**Table 2-1**, **Figure 2-1, Figure 2-2**).

PHARMACOKINETICS/PHARMACODYNAMICS[3]

Warfarin is a racemic mixture of R and S enantiomers that differ with respect to elimination half-life, metabolism, pathways of oxidative metabolism, and potency (**Table 2-2**). The pharmacokinetic and pharmacodynamic properties of other VKAs available outside the United States are quite different from those of warfarin (**Table 2-3**).

Pharmacogenomic characteristics influence warfarin dosing requirements in a number of ways.[4] Genetic variations in CYP2C9 genotype can influence the clear-

TABLE 2-1: Proteins and Half-life

Vitamin K Dependent Proteins	Elimination Half-life
Factor II	42–72 hr
Factor VII	4–6 hr
Factor IX	21–30 hr
Factor X	27–48 hr
Protein C	8 hr
Protein S	60 hr

TABLE 2-2: Differences in R and S Enantiomers

	R-Warfarin	S-Warfarin
Elimination half-life	45 hr (20–70 hr)	29 hr (18–52 hr)
Metabolism	40% reduction 60% oxidation	10% reduction 90% oxidation
Oxidative metabolism	1A2>3A4>2C19	2C9>3A4
Potency	1 (reference)	2.7–3.8 × R-warfarin

TABLE 2-3: Other K Antagonists

	Acenocoumarol	Phenprocoumon
Elimination half-life	**R:** 9 hr **S:** 0.5 hr	**R:** 5.5 days **S:** 5.5 days
Oxidative metabolism	**R:** 2C9>2C19 **S:** 2C9	**R:** 2C9 **S:** 2C9 1/3 eliminated unchanged
Potency	R more active due to faster clearance of S	S 1.5–2.5 × more potent than R

ance of warfarin, leading to lower-than-average warfarin dosing requirements in patients who are CYP2C*1/*2, CYP*1/*3, and CYP*2/*3 heterozygotes, and even lower dosing requirements in CYP*2/*2 and CYP*3/*3 homozygotes. The *2 and*3 alleles are the primary dysfunctional alleles in patients of European ancestry, and the *3 allele is most prevalent in patients of Asian ancestry. Additional polymorphisms, including *5, *6, *8 and *11 alleles, have been observed in patients of African ancestry.

Haplotype for VKORC1 influences warfarin responsiveness. A minor A allele in a specific regulatory region of VKORC1, with highest frequency