Pharmacogenomic Testing and Warfarin Management

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Warfarin has been used for the prevention of thrombosis for more than 50 years and is the most frequently prescribed vitamin K antagonist in North America (Gage & Eby, 2003). Its mode of action is to prevent vitamin K from converting to vitamin KH₂, thereby inhibiting clotting factors (Johnson & Cavallari, 2015). Warfarin metabolism is affected by variations in the cytochrome P450 2C9 (CYP2C9) and the vitamin K epoxide reductase complex 1 (VKORC1) genotypes. CYP2C9 affects the drug’s pharmacokinetics, or metabolism, whereas VKORC1, the target protein of warfarin, affects the drug’s pharmacodynamics, or its impact on cell proteins.

CYP2C9 variations can influence the dosage requirements of warfarin (Johnson & Cavallari, 2015). Most variations are caused by single nucleotide polymorphisms (SNPs) that lead to lower dosage requirements, with the exception of the CYP2C9*6 allele, which is a single nucleotide deletion. Individuals who are homozygous for the wild type allele CYP2C9*1 will typically have normal metabolism of warfarin. Individuals with one of the abnormal SNPs (i.e., either CYP2C9*2 or CYP2C9*3) metabolize warfarin more slowly and are prone to higher international normalized ratios (INRs) during the induction of warfarin therapy. These individuals are also about 2.6 times more prone to hemorrhage during the initiation of therapy than individuals with the normal allele (Gage & Eby, 2003). These two SNPs are the primary variations found in those of European descent and are found less often in people of African descent (Johnson & Cavallari, 2015). Other SNPs of CYP2C9 occur most often in people of African descent, and the presence of the CYP2C9*2 allele is rare in those of Asian descent.

In addition, the presence of the single polymorphism A allele of VKORC1 is associated with lower dosage requirements for warfarin and a higher risk of hemorrhage. The abnormal A allele is most commonly found in Asians followed by Europeans, and is least frequently seen in people of African descent. Although the FDA has approved some test kits for warfarin pharmacogenetic testing, the drug label does not overtly recommend the use of genotype results, the use of personalized medicine and pharmacogenomics to help identify optimal dosages for individual patients. However, the FDA (2007) also advised that when pharmacogenetic testing is used, it must be used cautiously and in collaboration with INR. The package insert for Coumadin®, a brand name for warfarin sodium, suggests that the initial and maintenance dosages of warfarin be adjusted depending on the presence of gene variations of CYP2C9 or VKORC1, if known (Bristol-Myers Squibb Pharmaceuticals Company, 2011). In a statement that announced the addition of genetic information to warfarin packaging, the FDA (2007) noted that it supports the use of personalized medicine and pharmacogenomics to help identify optimal dosages for individual patients. However, the FDA (2007) also explained that more studies are needed to determine the precise drug dosages for patients with genetic variations. Although the FDA has approved some test kits for warfarin pharmacogenetic testing, the drug label does not overtly recommend the use of genotype results.