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The Effects of CYP2C9 and VKORC1 on the Response of Warfarin in Korean Patients with Mechanical Heart Valve Replacement

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Aim: The primary objective of this study was to evaluate whether variability in warfarin dose requirements is related to polymorphism of VKORC1 and CYP2C9 in Korean population. Secondary objective was to determine whether polymorphism of VKORC1 and CYP2C9 are associated with time to reach the steady state of anticoagulation and bleeding risk.

Methods: We conducted a retrospective study in 198 Korean patients receiving long-term warfarin maintenance therapy with mechanical heart valve replacement. Genotyping for CYP2C9*1 and *3 and three VKORC1 variants, 1,173C>T, 1,181T>G (novel mutation in Korean population) were performed. The daily dose of warfarin, INR (international normalized ratio), concentrations of S-warfarin and S-7-hydroxywarfarin in plasma, metabolic ratio were used as pharmacokinetic and pharmacodynamic indices. Time to reach therapeutic INR range during loading period of warfarin, the first day above therapeutic INR range and stable dose, and the frequency of bleeding before steady state was evaluated using survival analysis.

Results: The patients with CYP2C9*1, VKORC1 1,173CT allele required the highest warfarin dose (5.86±1.55 mg/day), the patients with CYP2C9*3, VKORC1 1,173TT allele required the lowest warfarin dose (2.55±0.55 mg/day) and the patients with VKORC1 1,181TG allele, which is not detected in patient with CYP2C9*3, required lower dose of warfarin (3.31±0.09 mg/day) among CYP2C9*1 carriers. The time to reach the first day above therapeutic INR range are 543±207 and 8±2 days for CYP2C9*1 and *3 (P=0.0047), 145±50 and 2,124±613 days for VKORC1 1,173TT and 1,173CT (P=0.177), respectively.

Conclusions: CYP2C9*3 polymorphism contribute to lower warfarin dose, longer time to reach the steady state of warfarinization, increased risk of overanticoagulation, and VKORC1 1173CT polymorphisms are related to higher warfarin dose, lower frequency of bleeding, decreased risk of overanticoagulation in Koran patients with mechanical heart valve replacement. It needs to evaluate the contribution of the effect of VKORC1 1,181TG on the warfarin response in larger number of patients. Further studies with more patients are going on to validate these findings.

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