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Pharmacokinetic Model of Warfarin and Its Application in Personalized Medicine

Authors : Vijay Kumar Kutala, Addepalli Pavani, M. Amresh Rao, Naushad Sm

Abstract : In this study, we evaluated the impact of CYP2C9*2 and CYP2C9*3 variants on binding and hydroxylation of warfarin. In silico data revealed that warfarin forms two hydrogen bonds with protein backbone i.e. I205 and S209, one hydrogen bond with protein side chain i.e. T301 and stacking interaction with F100 in CYP2C9*1. In CYP2C9*2 and CYP2C9*3 variants, two hydrogen bonds with protein backbone are disrupted. In double variant, all the hydrogen bonds are disrupted. The distances between C7 of S-warfarin and Fe-O in CYP2C9*1, CYP2C9*2, CYP2C9*3 and CYP2C9*2/*3 were 5.81A°, 7.02A°, 7.43° and 10.07°, respectively. The glide scores (Kcal/mol) were -7.698, -7.380, -6.821 and -6.986, respectively. Increase in warfarin/7-hydroxy warfarin ratio was observed with increase in variant alleles. To conclude, CYP2C9*2 and CYP2C9*3 variants result in disruption of hydrogen bonding interactions with warfarin and longer distance between C7 and Fe-O thus impairing warfarin 7-hydroxylation due to lower binding affinity of warfarin.

Keywords : warfarin, CYP2C9 polymorphism, personalized medicine, in Silico
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