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A New Algorithm for Weekly Phenprocoumon Dose Variation in a Southern Brazilian Population: Role for CYP2C9, CYP3A4/5 and VKORC1 Genes Polymorphisms.

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Abstract

Phenprocoumon is widely used in prophylaxis and treatment of thromboembolic disorders. However, its pharmacokinetics and pharmacodynamics vary according to several genetic and non-genetic factors. Phenprocoumon metabolism is mediated by CYP2C9 and CYP3A enzymes. Moreover, VKORC1 is phenprocoumon target of action. Therefore, the aim of this study was to evaluate the association of single nucleotide polymorphisms (SNPs) in VKORC1, CYP2C9, CYP3A4 and CYP3A5 genes with the variance of weekly phenprocoumon dose as well as to develop an algorithm for dose prediction based on genetic and environmental factors. A total of 198 patients with stable phenprocoumon dose, 81% of European ancestry, were investigated. Genotypes were determined by allelic discrimination with TaqMan assays. Polymorphisms -1639G>A and 1173C>T in VKORC1 and the presence of CYP2C9*2 and/or CYP2C9*3 are associated with lower doses. On the other hand, 3730G>A in VKORC1 gene is associated with higher doses. No association was found between CYP3A4*1B, CYP3A5*3 and CYP3A5*6 polymorphisms. Among non-genetic factors, gender, height, age and use of captopril, omeprazole, simvastatin and β-blockers are associated with dose. Two algorithms were derived: one for the whole sample explained 42% of dose variation and one for patients of European ancestry only which explained 46% of phenprocoumon dose. The mean absolute difference between observed and predicted dose was low in both models (3.92 mg/week and 3.54 mg/week, for models 1 and 2, respectively). However, more studies with other genes and environmental factors are needed to test and to improve the algorithm.

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