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VKORC1 polymorphisms and warfarin maintenance dose in population of Sakha (Yakuts)

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BACKGROUND: Vitamin K antagonists are effective in the prevention and treatment of thromboembolic disorders. Warfarin is one of the most widely prescribed vitamin K antagonists in the world [1, 2]. It has a narrow therapeutic range and a given dose may result in a large inter-individual variation of response. Insufficient dose may fail to prevent thromboembolism, while an overdose increases the risk of bleeding. Patient-specific factors (e.g., age, body size, race, concurrent diseases, and medications) explain some of the variability in warfarin dosage, but genetic factors influencing warfarin response explain a significantly higher proportion of this variability [3]. Molecular analysis of the gene that encodes the target enzyme vitamin K epoxide reductase complex 1 (*VKORC1*) strongly suggests that its genetic variations greatly affect the individual response to oral anticoagulants [4–7].

OBJECTIVE: To evaluate effects of VKORC1 polymorphisms on warfarin dose excess anticoagulation (INR >4.0) in the population of Sakha (S) patients.

METHODS: 53 patients (29-women, 24-men) with atrial fibrillation (68%), congestive heart failure (60%), hypertension (49%) and cardiac valve replacement (26%) were recruited. The age range was 26–80 years, with a mean age of 62.87 ± 12.57 years.

International normalized ratio and plasma warfarin concentrations were determined. Genotyping was carried out by RT-PCR (real-time PCR). The three genetic polymorphisms of the gene *VKORC1* G3673A (rs9923231) were studied: normal *(GG)*, heterozygous *(GA)* and homozygous *(AA)*. Fisher exact probability test and chi-square test (with Yates correction) were applied to compare data among the *AA* and *GG* + *GA* groups; also Mann-Whitney test was used.

RESULTS: The median maintenance daily dose of warfarin among *AA* carriers was 3.0 mg/day [1.25–7.5 mg], while in *GG* and *GA* patients it was 3.13 mg/day [1.88–7.92 mg]. The mean daily warfarin dosage was higher in *GG* and *GA* genotype carriers 4.05 mg/day (SD ± 1.7) than in patients with *AA* genotype 3.13 (SD ± 1.5). Differences are of borderline significance ($p = 0.054$).

Of the 41 patients who required warfarin doses of less than 5 mg, 28 (63%) were found to be *AA* carriers and 14 (37%) were GG, GA carriers. Differences were not quite significant ($p = 0.072$). Among 31 homozygous polymorphism carriers 2 (4%) patients developed overanticoagulation (INR >4.0), while among 22 normal and heterozygous polymorphisms carriers only 3 (6%) patients developed overanticoagulation (INR >4.0). Differences were not statistically significant ($p = 0.36$).

CONCLUSIONS: No significant association between *VKORC1* polymorphisms and the frequency of excess anticoagulation (INR >4.0) was found. This may be explained by the number of cases included. *AA* polymorphisms compared to other polymorphisms shows borderline difference in the warfarin dose. The results can be used for the development of a pharmacogenetic-guided warfarin dosing algorithm.

Keywords: Polymorphisms of the VKORC1 gene on maintenance warfarin dose in the population of sakha (yakuts)

Conflict of interest statement: None.

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