International Journal of Risk & Safety in Medicine 27 (2015) S15–S16
DOI 10.3233/JRS150672
IOS Press

ABCB1 polymorphism and acenocoumarol safety in patients with valvular atrial fibrillation

A. Rozhkov[a]*, D.A. Sychev[b] and R.E. Kazakov[a,c]

[a]*I.M.Sechenov, First Moscow State Medical University, Moscow, Russia*
[b]*Russian Medical Academy of Postgraduate Education, Moscow, Russia*
[c]*Federal State Institution Scientific Center of Medical Products Expertise, Moscow, Russia*

*Corresponding author. E-mail: rozkovsaha@mail.ru

BACKGROUND: Oral anticoagulant drugs (AD) are commonly used to treat patients with thromboembolic diseases. The ADs have narrow therapeutic index and wide pharmacokinetic and pharmacodynamic interindividual variability. Some genetic variations could influence interindividual variability in response to AD. Acenocoumarol (AC) is a coumarin, vitamin K derivate with antagonistic activity, used as anticoagulant therapy mainly in Central Europe and Latin America. P – glycoprotein (PGP), a transporter encoded by the ABCB1 gene, plays a major role in the drug disposition [1]. PGP is expressed in normal tissues, where it performs a defensive role against potentially toxic substances in intestinal cells and endothelial cells of the brain capillary endothelium. ABCB1 – is highly polymorphic, C3435T polymorphism in exon 26 has been associated with the expression of PGP [2]. There is some evidence that PGP could influence coumarin sensitivity.

OBJECTIVE: To assess effects of the ABCB1 pilymorphisms on safety profile and dosing regimen of acenocoumarol in the patients with valvular atrial fibrillation.

METHODS: 50 patients (34 male and 16 female), 40–70 years of age were included. All patients received acenocoumarol at doses of 1–6 mg daily with a target international normalized ratio (INR) of 2.0 to 3.0. Genotyping for polymorphism marker C3435T of ABCB1 gen was performed using PCR and RFLP (restriction fragment length polymorphisms) techniques. Statistics were performed by Fishers exact tests. All enrolled patients provided written informed consent.

RESULTS: Genotype CC was found in 10 patients (20%), genotype CT in 25 patients (50%) and genotype TT in 15 patients (30%). In the CC group ($n=10$) bleeding was found in 1 patient (2%). There were 19 patients (38%) with bleedings in combined group of CT and TT genotype ($p=0.0366$). We compared the average doses of acenocoumarol in groups identified according to their genotypes: CC (3.45 mg/day), CT (2.64 mg/day), TT (3.07 mg/day) and found no significant differences.

CONCLUSIONS: ABCB1 CT and TT genotypes were found to be significantly associated with higher risk of bleeding. There was no influence of ABCB1 polymorphisms on dosing regimens of acenocoumarol.

Conflict of interest statement: The authors report no conflicts of interest.

Keywords: ABCB1 polymorphism, acenocoumarol, safety, valvular atrial fibrillation, bleeding

References

[1] Ling V. Multidrug resistance: Molecular mechanisms and clinical relevance. Cancer Chemotherapy and Pharmacology 1997 Vol 40(Is.1):S3-S8. doi: 10.1007/s002800051053
[2] Hoffmeyer S, Burk O, von Richter O. Functional polymorphisms of the human multidrug – resistance gene: Multiple sequence variations and correlation of one allele with P – glycoprotein expressions activity in vivo. Proc Natl Acad Sci USA 2000;97(7):3473-8. doi:10.1073/pnas.050585397
[3] De Oliveire Almeida VC, Ribeiro DD, Gomes KB, Godard AL. Polymorphisms of CYP2C9, VKORC1, MDR1, APOE and UGT1A1 genes and the therapeutic warfarin dose in Brazilian patients with thrombosis: a prospective cohort study. Mol Diagn Ther. 2014;18(6):675-83. doi: 10.1007/s40291-014-0121-4