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Effects of CYP2C9 and VKORC1 polymorphisms on acenocoumarol sensitivity and responsiveness during the postoperative period after cardiac surgery

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PURPOSE / OBJECTIVES

Cardiac surgery is associated with an inflammatory response promoting a hypercoagulable state, which requires successful postoperative anticoagulation. Acenocoumarol, an oral vitamin K antagonist, is a commonly prescribed anticoagulant following cardiac surgery. Our aim was to investigate the influence of genotype variants at two loci responsible on acenocoumarol metabolism.

MATERIALS & METHODS

200 post-op patients given acenocoumarol thromboprophylaxis were reviewed for INR values on the first five days of acenocoumarol treatment. Genotyping for VKORC1 1639G>A and CYP2C9*2&*3 polymorphisms were done by RT-PCR. Significant differences among genotypes in INR were assessed.

RESULTS

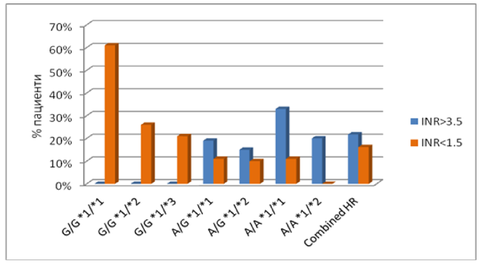

Figure 1. Distribution of “hyperreactive” (INR>3.5) and “suptherapeutic” (INR<1.5) responders on the 3th day of the therapy.

No specific factor, including age, gender, BMI, tobacco use, type of operation, or medication regimen, was disproportionally represented in any genotypic group, preventing the need to adjust INR values.

Genotype distribution for VKORC1 and CYP2C9 was G/G*1/*1–24.5%, G/G*1/*2–9.5%, G/G*1/*3– 7%, A/G*1/*1–27%, A/G*1/*2–10%, A/A*1/*1– 9.5% and A/A*1/*2–5%.

Comparison of INR revealed no significant differences among genotypic groups on days one (p = 0.35) and five (p = 0. 51). Differences in INR were detectable by day three (p = 0.02). Normal responders were more likely to be subtherapeutic with INR<1.5 (p<0.05) compared to those with mutant genotype. Genotypes A/G*1/*1, A/G*1/*2, A/A*1/*1 and A/A*1/*2 are associated with a higher incidence of "hyperreactive” results (INR> 3.5) and a higher risk of bleeding.

The comparison of normal responders (n = 82) to the collective cohort of hyperresponders (n = 103) revealed that the former group had both a significantly lower INR (p= 0 .006) and carried higher relative risk being subtherapeutic (61% vs. 16.2%, P < 0 .001) on the third day of acenocoumatol treatment.

RESULTS

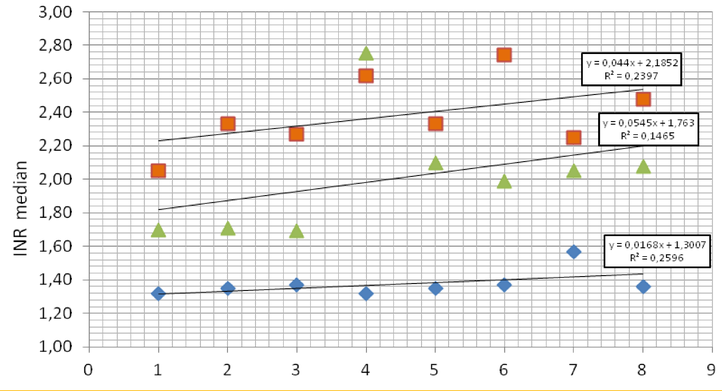

Figure 2. Linear regression of INR profiles on the first (blue), the third (red) and fifth (green) day postoperatively, stratified by genotype.

CONCLUSION

Presence of a mutant allele of VKORC1 1639G>A and CYP2C9 *2 and *3 increased the odds of requiring a lower mean dosage of acenocoumarol. Wild-type patients at both loci had yet to reach therapeutic INR or being subtheraputic by day three more frequently than those with mutation variants. The study was done with a financial support of Medical University Sofia, contract No:D-239/19.12.2019.

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