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Research Article

The impact of CYP2C9 and VKORC1 genetic polymorphisms in anticoagulant therapy management after cardiac surgery with extracorporeal circulation

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Abstract

Extracorporeal circulation during cardiac surgery is characterized with increased risk for hypercoagulation because blood is exposed to foreign, nonendothelial cell surfaces. Thus, the usage of extracorporeal circulation is essentially not possible without anticoagulation. Open-heart surgery as well as many perioperative factors, such as acidosis, hypocalcemia, hypothermia, and hemodilution, might affect hemostasis and lead to coagulopathy and bleeding. A new insight into the effectiveness of anticoagulant therapy is applied to modify the dosing regimen with respect to the genetic CYP2C9 and VKORC1allelic variants. A systematic literature search was performed for VKORC1 and CYP2C9 and their association with coumarin anticoagulant therapy and bleeding risk in postoperative period of cardiac surgery with extracorporeal circulation.

Keywords

Anticoagulants, bleeding, CYP2C9, extracorporeal circulation, pharmacogenetics, VKORC1

Introduction

During cardiac surgery with extracorporeal circulation, the coagulation system undergoes major changes since blood exposed to foreign, nonendothelial cell surfaces is collected and continuously recirculated throughout the body. This contact with synthetic surfaces within the perfusion circuit, as well as open tissue surfaces, results in a hypercoagulable state. Cardiac surgery patients are unique because therapeutic anticoagulation is required during and after extracorporeal blood circulation procedure. Pathophysiology of hemostasis abnormalities with extracorporeal circulation is related to an excessive bleeding risk and an inflammatory response promoting a hypercoagulable state (Despotis et al. 2001; Sniecinski and Chandler 2011). Multiple factors should be taken into consideration for the successful management of postoperative anticoagulant therapy, such as patient characteris-

tics (indications, age, renal function, patient history of bleeding or thromboembolic complications) and surgical factors (hemodilution, acquired platelet dysfunction, coagulation factor consumption, hypocalcaemia (Ho and Yip 2016) systemic hypothermia (De Robertis et al. 2015), acidosis (Ranucci et al. 2015) and blood loss during surgery) (Vonk et al. 2013; Varnai et al. 2017).

Coumarin oral anticoagulants (COA), such as warfarin, acenocoumarol and phenprocoumon, are vitamin K antagonists and have proven to be effective for the prevention of thrombotic events. They are the most commonly used oral anticoagulants by patients with atrial fibrillation undergoing cardioversion, prosthetic heart valves, deep vein thrombosis, pulmonary embolism and post extracorporeal circulation cardiac surgery. Narrow therapeutic index drugs, such as COAs require highly individualized dose adjustment with consideration to the proper therapeutic INR range for each particular patient (Kaur et al 2013; Lee et al. 2020). Strict control of INR levels is mandatory in order to reduce the risk of thrombosis by underanticuagulation or bleeding by overanticoagulation (Varnai et al. 2017; Cullell et al. 2018). In plasma, COAs are bound primarily to albumin. Therefore, in cases of hypoalbuminemia their free fraction increases resulting in potentiating of their anticoagulant effects (Kawai et al. 2019).

COAs inhibit the vitamin K-dependent synthesis of biologically active clotting factors. Warfarin is the most potent COA and is widely used worldwide, while acenocoumarol (Sintrom) and phenprocoumon (Marcumar) are more common in Europe (Pengo et al. 2006; Beinema et al. 2008; AL-Eitan et al. 2019).

Pharmacogenetics and pharmacogenomics aim to establish the influence of genetic factors on monitoring of drug efficacy and adverse drug reactions (Lee et al. 2020). The response to COAs differs at initiation and in the course of therapy and varies from patient to patient. The individual reactivity to COAs is among the most frequently cited causes of drug-dependent mortality (Verstuyft et al. 2012; Lee et al. 2020). In about half of the patients, the anticoagulant effects are influenced by clinical factors, environmental and lifestyle factors such as age, weight, sex, smoking and many drugs (Brunner-Ziegler et al. 2014), which inhibit or induce the CYP2C9 enzyme (Wolkanin-Bartnik et al. 2018). In other cases, genetic factors, especially gene polymorphisms of VKORC1, CYP2C9, and the rs12777823 variant of CYP2C are associated with lower dose requirements because of a higher risk of major bleeding (Verhoef et al. 2014). A variation in another gene, CYP4F2, has been associated with slightly increased COA dose requirements in European and Asian population. However, this variation is not included in any validated pharmacogenetic algorithm for calculation of COA dosing.

Genetic polymorphisms are minimal changes in genetic information, present in more than 1% of the population, considered to be normal variants, but nevertheless, in certain circumstances, they can contribute to phenotypic differences, including increased disease risk and altered drug response (Cullell et al. 2018). Genetic polymorphisms make an important contribution to the great inter-individual and inter-ethnic variability in anticoagulant therapy response (Wolkanin-Bartnik et al. 2013; Misasi et al. 2016). Due to the fact, that patients underwent extracorporeal circulation surgery are exposed to increased risk for thrombosis, the persistently subtherapeutic anticoagulation may lead to thromboembolic events, but on the other hand, supratherapeutic anticoagulation can lead to bleeding, both of which with a possible poor outcome (Despotis et al. 2001; Farzamikia et al. 2017).

Variant VKORC1 and CYP2C9 alleles have been shown to be the most important genetic determinants that affect the pharmacokinetics and pharmacodynamics of vitamin K antagonists (Cullell et al. 2018). Coumarins directly inhibit VKORC1, while CYP2C9 is the enzyme metabolizing COAs, thus determining their bioavailability and principally responsible for their anticoagulant effect. Polymorphisms in VKORC1 and CYP2C9 account for about 40% of the interindividual variability in dose requirements and the therapeutic response (Van Schie et al. 2009; Biswas et al. 2018). Polymorphisms in other genes, some of which have not yet been identified, have minimal or no effect on COA metabolism (Tatarunas et al. 2014; Cullell et al. 2018).

The role of VKORC1 in COA metabolism

VKORC1 (Vitamin K epoxide reductase complex subunit1) gene encodes the synthesis of the enzyme vitamin K epoxide reductase 1 (VKORC1). The enzyme VKORC1 is a membrane protein localized primarily in hepatocytes. It assists the conversion (activation) of coagulation proteins involved in the formation of the hemostatic thrombus. COAs directly inhibit the activation of the VKORC1 enzyme, thus delaying the activation of coagulation proteins (Cimpan et al. 2019).

Some VKORC1 gene polymorphisms reduce the amount of the functional VKORC1 enzyme required for the activation of clotting proteins. The most common VKORC1 gene polymorphism, known as VKORC1A, is a single nucleotide change in the promoter region of VKORC1 resulting in an alteration of transcription factor binding site. In particular, the nucleotide guanine is replaced by adenine (-1639G> A, rs9923231). This leads to reduced synthesis of functional VKORC1 protein, which is needed to convert vitamin K into a form that is able to activate coagulation proteins. The carriers of this polymorphism respond to lower doses of COAs and are at higher risk of COA-related adverse events (Misasi et al. 2016; Varnai et al. 2017; Chaidaroglou et al. 2019; Cimpan et al. 2019).

The role of CYP2C9 in COA metabolism

The CYP2C9 gene encodes the synthesis of an enzyme localized in the endoplasmic reticulum of cells that plays a major role in a protein transport and the breakdown

(metabolism) of steroid hormones, drugs (including COAs) and fatty acids (Misasi et al. 2016). Probably the best studied substrate of CYP2C9 is S-warfarin, which is 5 times more potent than R-warfarin (Warfarin is a racemic mixture of the two isomers S-warfarin and R-warfarin). S-warfarin is metabolized almost exclusively to 7-hydroxywarfarin by a highly polymorphic hepatic enzyme, CYP2C9, while the metabolism of R-warfarin is accomplished via CYP1A2 and CYP3A4 R. Functionally significant gene polymorphisms causing impaired metabolic capacity of CYP2C9 have been associated with increased COA response and lower dose requirements (Varnai et al. 2017; Chaidaroglou et al. 2019; Cimpan et al. 2019).

The most common CYP2C9 genetic variants in the European population associated with hypersensitivity to COA, are CYP2C9 * 2 and CYP2C9 * 3 (Samiee et al. 2014). Homozygotes *2/*2 have approximately 12%, while homozygotes *3/*3 have <5% of normal CYP2C9 activity (Chaidaroglou et al. 2019). This requires the use of 1/3 to 1/4 lower than usual doses for COA treatment (Misasi et al. 2016; Sridharan et al. 2016; Chaidaroglou et al. 2019). According to published studies, patients treated with COA at doses consistent with their specific genotype sensitivity achieved stable INR levels much earlier than those with an unknown genetic profile (Yang et al. 2013; Chaidaroglou et al. 2019; Cimpan et al. 2019).

Studies have shown that the CYP2C9*2 and *3 alleles trouble the formation of intermediate components of the CYP2C9 enzyme catalytic cycle, leading to significantly reduced enzyme activity (Wei et al. 2007). As a result, the clearance of COA was reduced by about 40% for genotype CYP2C9 *1/*2 (c.C430T; p.Arg144Cys, rs1799853), up to 75% with genotype *1/*3 (c.A1075C; p.Ile359Leu, rs1057910) and up to 90% with genotype *3/*3 (Daly et al. 2017). In rare cases, more than one polymorphism in CYP2C9 might be detected, leading to highly limited enzyme activity and an increased risk of COA overdose (Wei et al. 2007; Sánchez-Diz et al. 2009; Kaur et al. 2013).

In their study of 6232 patients on COA therapy, after stratification of the risk for hemorrhagic events, Yang et al. (2013) demonstrated that there was a significantly higher risk in the carriers of at least one copy of the CYP2C9 *3 allelic variant. In two other studies, Wolkanin-Bartnik et al (2013) and Kaur et al. (2013) have linked the variant CYP2C9 genotype to an increased risk of major postoperative hemorrhage that persisted even after stabilization of therapy.

Pharmacogenetic monitoring of COA therapy

The influence of polymorphisms in CYP2C9 and VKORC1 on the response of all three coumarin derivates is relatively equal and is most significant during initiating anticoagulation (Pengo et al. 2006; Dean 2015; Baranova et al. 2017). On the other hand, they markedly affect the long-term monitoring of anticoagulant effects. The presence of CYP2C9 polymorphism is associated with delayed stabilization of the anticoagulant response, whereas VKORC1 polymorphisms cause an increased risk of bleeding, especially in postoperative patients (Kaur et al. 2013; Baranova et al. 2017; Farzamikia et al. 2017).

The main challenge in COA treatment is to achieve a stable long-term anticoagulant response in the presence of a narrow therapeutic "window" because small changes in plasma levels may lead to supra-optimal concentration-dependent side effects or insufficient anticoagulant response. The dosage of COA is strictly individual and should be monitored according to the therapeutic response measured by the International Normalized Ratio (INR) (Baranova et al. 2017). A study of post mitral valve surgery patients conducted by Farzamikia et al. (2017) demonstrated that carriers of the CYP2C9 * and VKORC1 -1639G (1) alleles (both normal, wild-type) required higher doses of COA, while those with CYP2C9 variants *2 and *3 and VKORC1 -1639A required lower doses. The same conclusions were reached by Tatarunas et al. (2014), who found that patients with CYP2C9*2 and *3 allelic variants achieve satisfactory INR with much lower doses, even half doses of COA, compared to those without the mutant allele.

The effect on INR is usually established 24 hours after initiation of therapy, but the complete anticoagulant response may be delayed for 5–7 days due to the long half-life of prothrombin (approximately 60 hours) (Beinema et al. 2008; Verhoef et al. 2014). COAs are rapidly and completely absorbed after oral administration, and their absorption is not affected by food. In blood, they circulate bound to albumin (97%) and only the unbound form is biologically active. This suggests a reduction in daily and weekly doses in hypoalbuminemia (malnutrition, advanced liver disease, postoperative conditions, etc.). In the postoperative period after cardiac surgery and extracorporeal circulation, the recommended target values of INR for achieving a good anticoagulant response are 2 <INR <3.5 (Bryk et al. 2018).

About 10% to 30% of patients taking COA do not achieve a stable anticoagulant effect, which increases the risk of thrombotic events or bleeding (Verhoef et al. 2014; Sridharan et al. 2016). Bleeding is the most serious complication of COA treatment, with a significantly increased risk when INR is > 4 and it depends largely on comorbidity, the use of certain medications, and the concomitant use of antiplatelet therapy. The average annual incidence was estimated at 0.6% for fatal, 3.0% for large and 9.6% for small hemorrhages (Crowther and Warkentin 2008).

Patients with VKORC1 gene polymorphisms are classified as „poor metabolizers" of COA and are at increased risk of overdose and subsequent major hemorrhages (cerebral or extracerebral haemorrhages, decrease in hemoglobin concentration of 20 g/L or more and eventually the need of blood transfusion) (Misasi et al. 2016; Sridharan et al. 2016; Bryk et al. 2018).

The incidence of hypersensitivity to COA has not been well established, but Misasi et al. (2016) reported that it is more common in older patients and in patients with lower body weight.

COA resistance

Some of the multiple variations in the VKORC1 gene are associated with increased resistance to COA, a condition that requires the use of higher COAs than doses normally prescribed (Wzorek et al. 2018; Kaur et al. 2013). COA resistance can be classified as acquired (poor patient compliance, food sources with higher amount of vitamin K, interactions with medications) versus hereditary.

The most common VKORC1 genetic variants in coumarin-resistant people is identified as a coding polymorphism resulting in replacement of the amino acid aspartame with tyrosine at 36th place in the structure of the VKORC1 enzyme (designated as an Asp36Tyr or D36Y) (Watzka et al. 2010). This structural change reduces the binding capacity of the enzyme VKORC1 to coumarin anticoagulants, which predetermines the use of higher than usual doses to inhibit VKORC1 activity. Unlike hypersensitivity, it is difficult to achieve reliable anticoagulant effect in COA resistant patients and the risk of clot formation remains relatively higher (Anton et al. 2013; Cimpan et al. 2019).

Two types of COA resistance have been identified – incomplete and complete. In patients with incomplete resistance, the expected therapeutic target is achieved with the usage of higher doses of COA (Wzorek et al. 2018; Kaur et al. 2013). Complete resistance is characterized by minimal or no response even at very high doses of coumarin anticoagulants. Genetically determined resistance to COA is considered to be a relatively rare finding.

Conclusion

Recent studies have shown that CYP2C9 and VKORC1 gene polymorphisms are important for individualizing treatment and applying a personalized anticoagulant therapeutic approach, with genotyping predicting about 50% of the interindividual variation in the anticoagulant pharmacodynamic response. Adjustment of the genotype-guided dosing algorithm for anticoagulant therapy in postoperative period of patients undergoing extracorporeal circulation cardiac surgery could lead to improved patient care.

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