Pharmacogenetics of oral anticoagulant therapy

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Oral anticoagulant therapy (OAT) based on coumarins (warfarin, Coumadin) and other vitamin K antagonists (acenocoumarol, Syntrom) has been the cornerstone of prevention and treatment of several thrombotic disorders, and these compounds are still the most used anticoagulant medications worldwide. Warfarin is a racemic mixture of two optically active enantiomers; S-warfarin is prevalently metabolized by the CYP2C9 enzyme of the cytochrome P450 system, whereas R-warfarin is cleared by the two cytochrome enzymes 1A2 and 3A4 (CYP1A2 and CYP3A4). Warfarin and other coumarins produce their anticoagulant effect by contrasting the cyclic inter-conversion of vitamin K to its 2,3 epoxide. The enzymes vitamin K epoxide reductase (VKOR) and vitamin K reductase are essential in this process, because they reduce the vitamin K 2,3-epoxide to the active vitamin K quinole cofactor.

The management of OAT is difficult, due to considerable variability in the dose-response which can be ascribed to environmental, demographical, clinical and genetic variables. Predicting individual responses to the therapy represents a major challenge, and patients may be exposed to adverse heath outcomes from bleeding or thrombosis due to over- and undercoagulation. However, several lines of evidence indicates that up to 60% of the individual pharmacological response might be genetically regulated and influenced by single nucleotide polymorphisms in the genes encoding VKOR and cytochrome P450 CYP2C9. Therefore, genetic testing is currently regarded as a promising tool to help predict dose response during initial anticoagulation, assess dose maintenance variability, and identify warfarin resistance. Nevertheless, pharmacogenetics of OAT can not be considered as yet the "magic bullet", current limitations including a suitable organization of genetic panels, a limited amount of information about inter-individual variability, a lack of analytical and quality specifications, a partial availability of outcome analyses that unequivocally confirm cost-effectiveness, a lack of universal agreement related to reliable dosing algorithms and other ethical and social issues. Therefore, it seems reasonable to conclude that it is premature to introduce routine OAT pharmacogenetics in the daily practice, though the development and clinical validation of simple but comprehensive algorithms integrating the most informative gene polymorphisms, along with demographical (age, race, body mass index) and clinical variables (comorbidities, drugs interference) as well as a standardized dietary intake of vitamin K, may provide a valuable tool in the individually managed care of patients on OAT. It is also to consider that the forthcoming commercialization of new anticoagulant drugs targeting thrombin and factor X will introduce a paradigm shift in long-term anticoagulation therapy, where consideration could be given to demise pharmacogenetics testing for OAT.

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