Efficacy and safety of the indirect anticoagulant warfarin in its dosage based on the results of pharmacogenetic testing

Eficacia y seguridad del anticoagulante indirecto warfarina en su dosificación según los resultados de las pruebas farmacogenéticas

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Abstract

Abstract. Thrombotic complications are one of the main causes of death and disability, causing enormous economic damage to the state. There is an increase in the number of patients at high risk of these complications. The main aim of the article is to investigate efficacy and safety of the indirect anticoagulant warfarin in its dosage based on the results of pharmacogenetic testing. To achieve that aim, the use of drugs (JIC) from the group of indirect oral anticoagulants (ACND) is the only and uncontested method of long-term outpatient prevention of thrombosis - their effectiveness has been proven in primary and secondary prevention of thromboembolic complications in patients with atrial fibrillation and, above all, ischemic stroke. AKND therapy reduces the risk of all strokes by an average of 62%. The advantage of AKND therapy has been proven in terms of preventing primary and recurrent thromboembolism.

Keywords: indirect anticoagulant warfarin, cardiology, anticoagulant, patient, application.

Resumen

Resumen. Las complicaciones trombóticas son una de las principales causas de muerte y discapacidad, causando un enorme daño económico al estado. Hay un aumento en el número de pacientes con alto riesgo de sufrir estas complicaciones. El objetivo principal del artículo es investigar la eficacia y seguridad del anticoagulante indirecto warfarina en su dosificación basándose en los resultados de las pruebas farmacogenéticas. Para lograr ese objetivo, el uso de fármacos (JIC) del grupo de los anticoagulantes orales indirectos (ACND) es el único método indiscutido de prevención ambulatoria a largo plazo de la trombosis, cuya eficacia ha sido probada en la prevención primaria y secundaria de las complicaciones tromboembólicas. en pacientes con fibrilación auricular y, sobre todo, ictus isquémico. La terapia AKND reduce el riesgo de todos los accidentes cerebrovasculares en un promedio del 62%. Se ha demostrado la ventaja de la terapia con AKND en términos de prevención de tromboembolismo primario y recurrente.

Palabras clave: anticoagulante indirecto warfarina, cardiología, anticoagulante, paciente, aplicación.

Introduction

Therapy with AKND is extremely important for patients with prosthetic heart valves, the high risk of thromboembolic complications in which increases dramatically with atrial fibrillation. It has been shown that the reduction in the risk of thromboembolic complications in the treatment of AKND is 75%[1-3]. At the same time, it was found that the need for AKND therapy increases with age, as does the risk of thrombosis[4].

Selection of an individual dose of AKND and further maintenance of the required level of coagulation is achieved by laboratory monitoring of therapy. Currently, the method of monitoring the indicator of the international normalized ratio (INR) has been established[5,6]. This method is based on the proven relationship of the INR index with episodes of hypocoagulation in people taking AKND.

Despite all the accuracy of laboratory control and the availability of careful dose selection schemes, the main danger in prescribing AKND remains the possibility of bleeding. Hemorrhages occur with a frequency of up to 26%, of which "large" (ie leading to death, hospitalization or its prolongation), incl. fatal - up to 4.2%[6,7]. Of the 700 thousand patients with atrial fibrillation receiving warfarin daily, 17 thousand develop bleeding, which in 4 thousand cases is fatal[2,8]. The risk of developing bleeding directly depends on the level of INR and increases by 1.37 times with every 0.5 units of its increase[9]. In this case, an asymptomatic increase in INR can occur not only at the stage of saturation of the AKND, but also with prolonged use[2,3]. Therefore, it seems relevant to study the factors that determine individual sensitivity to AKND. One of these factors is the patient's genetic makeup.

Most AKNDs are metabolized by cytochrome P-450 isoenzymes CYP2C9. For this protein, alternative isoforms CYP2C9 * 2 and CYP2C9 * 3) are known, characterized by a significant decrease in activity[9,10]. Another important genetic factor that determines the change in the individual patient's response to AKND therapy is the genetic polymorphism of the 1st subunit of vitamin K epoxy reductase (VKORC1), the target molecule of all AKND.

It is assumed that the use of a personalized approach based on the results of pharmacogenetic testing to the dosage of AKND can help reduce the risk of hemorrhagic complications[2,7]. It is obvious that the introduction of such an approach will make it possible to more widely use AKND in patients who need them, by increasing the safety of treatment with these drugs. Despite the importance of the issue, its practical implementation is not possible without obtaining the results of prospective studies confirming the advantages of the pharmacogenetic approach to the selection of an individual dose of warfarin over the traditional one, which have not been previously performed in Russian patients.

Methods

Derivatives of indoandione (phenindione) and coumarin (warfarin, neodikumarin, acenocoumarol) form a group of drugs - indirect oral anticoagulants or vitamin K antagonists. At present, AKND occupies a leading position as drugs of choice for the prevention of thromboembolic complications of cardiovascular diseases. These drugs have a "good" evidence base, which determines their widespread use in the treatment and prevention of diseases of the cardiovascular system. In particular, the effectiveness of AKND has been proven for the primary and secondary prevention of thromboembolic complications in patients with atrial fibrillation and ischemic stroke itself, as the most frequent of them (91% of all cases - Framingham, Shibata, Whitehall). Analysis of the pooled database of studies on antithrombotic therapy versus placebo showed that therapy with AKND, and in particular with warfarin, reduced the risk of all strokes more effectively (by 62%) compared with acetylsalicylic acid (22%)[6-8] ... The ACTIVE-W study (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) has proven the benefits of ACND therapy in terms of preventing primary and recurrent thromboembolism over antiplatelet agents (clopidogrel) in combination with acetylsalicylic acid.

It has also been proven that AKND therapy remains an extremely important and mandatory indication in persons with prosthetic heart valves, in whom the high risk of thromboembolic complications increases sharply when they develop atrial fibrillation. A meta-analysis by Cannegieter (1994), which included more than 13,000 patients with artificial heart valves, showed that the reduction in the risk of thromboembolic complications with ACND therapy is 75%[10].

Results and Discussion

The traditional approach to dosing of indirect oral anticoagulants.

The extreme unpredictability of the effect of AKND at a fixed dosage determines the need for coagulation control when using them. There are different methods of such control, one of them is the "Quick's thromboplastin test (1937)", in accordance with the WHO recommendations (1981, 1999). The main disadvantage of this method is the need to construct a calibration curve, in comparison with the norm, it requires the use of a highly standardized normal control plasma.

The traditional algorithm for selecting the dose of warfarin.

To date, the INR (International Normalized Ratio[2,10]) monitoring method is used throughout the world for coagulation control when using AKND. The main criterion for its correctness can be considered the use of the MIC value (the international sensitivity index of the thromboplastin used from 0.7 to 1.1). Express methods have been developed for determining INR when taking a small amount of capillary blood. Numerous clinical studies have found a balance between effective therapy and the risk of complications. It is expressed in three ranges of INR values - from 2.0 to 3.0 (for all patients, including those with atrial fibrillation), from 2.5 to 3.5 (for patients with heart valve prostheses and / or with atrial fibrillation). arrhythmia), and in some cases, from 1.8 to 2.0 (if the patient is over 70 years old). The dosage of drugs used to achieve these INR levels varies significantly from person to person, largely due to multiple individual patient parameters such as age, gender, physique, comorbidities, diet, therapy received, genetic variation in metabolism, etc.

Problems with the use of indirect oral anticoagulants.

In a study conducted at the Institute of Clinical Cardiology. A.L. Myasnikov, in two groups of patients (70 people each) taking warfarin and acenocoumarol, an asymptomatic increase in INR was found, recorded at different stages of therapy, in 11.4% and 48.6%, respectively[3-5]. In many studies, it is possible to trace the presence of a significant percentage of bleeding occurring in the INR range from 2.0 to 3.0 - this corresponds to the most common therapeutic range. According to the same authors, with the use of two AKND - acenocoumarol and warfarin, the development of hemorrhagic complications was noted both with an increase in INR and with

therapeutic values of the indicator (the frequency of all hemorrhages was 25 and 20% per year for acenocoumarol and warfarin, respectively).

The incidence of hemorrhagic complications with therapeutic values of INR in both groups did not differ significantly. In these observations, attention was drawn to patients with recurrent bleeding occurring within a period of up to three years of therapy with acenocoumarol against the background of INR, which is within the therapeutic range (from 2.0 to 3.0).

From the above, we can conclude that, despite all the measures taken, the risk of bleeding during treatment with AKND remains high. Therefore, the study of the patient's individual sensitivity to drugs of this group remains relevant. Along with the above factors, the continuation of the study of the individual sensitivity of patients to AKND therapy in terms of genetic polymorphism may be of great practical interest.

Genetic factors affecting therapy with indirect oral anticoagulants.

Currently used in clinical practice, AKND (warfarin, acenocoumarol and phenprocoumon) are produced in the form of racemic mixtures of the S- and R-enantiomers. These enantiomers are metabolized by various cytochrome P-450 isoenzymes and differ significantly in anticoagulant activity (S-warfarin is 5 times higher than the anticoagulant activity of R-warfarin)[3,4]. It is known that the main enzyme of biotransformation of AKND is the isoenzyme of cytochrome P-450 CYP2C9, which carries out the process of hydroxylation of the S-enantiomers of all three aforementioned coumarin derivatives, as well as R-acenocoumarol and, to a lesser extent, R-phenprocoumon. In turn, R-warfarin is hydroxylated with the formation of inactive metabolites with the participation of isoenzymes CYP1A1, CYP2C19, CYP1A2. R-phenprocoumon is metabolized by CYP3A4. The anticoagulant effect of warfarin and phenprocoumon is mainly due to the pharmacological action of its S-enantiomers. The anticoagulant effects of S and R-acenocoumarol are comparable. Nevertheless, despite the differences in the biotransformation of the S- and R-enantiomers, it is generally accepted that it is the activity of CYP2C9 that mainly determines the rate of biotransformation of AKND, especially warfarin. As a consequence, changes in the activity of CYP2C9 under the influence of various factors can lead to clinically significant changes in the concentration of warfarin in blood plasma[2,8].

Algorithms for dosing warfarin, taking into account the results of pharmacogenetic testing.

To date, it is estimated that since the beginning of the development of pharmacogenetic tests, more than 21 thousand various recommendations have been issued regarding the personalization of pharmacotherapy with their help[8,9].

With the traditional approach to the use of AKND, the initial dose of, for example, warfarin is 5 mg / day. Further, the INR indicator is regularly measured, over the next 4-5 days, the dosage does not change significantly and remains at this level. It has been shown that during the period of "saturation" with warfarin in patients with different alleles of the CYP2C9 gene, including those with "functional defective", there are no significant differences in dosage (the first 5 days of therapy)[3-6]. Thus, the use of pharmacogenetic tests in the clinic can be recommended precisely during this period of time.

Based on the results of numerous studies on the pharmacokinetics of S-warfarin, graphs were obtained, reflecting the dependence of the concentration of S-warfarin on the time of selection of the individual dose of a given AKND in patients with different genotypes at the CYP2C9 locus with different dosing algorithms.

Advantages of the pharmacogenetic approach to warfarin dosing over the traditional one.

Currently, reducing the risk of medical complications when using a pharmacogenetic personalized approach to dosing warfarin is a clearly proven fact. The experience of some developed countries also shows the economic efficiency of the existence of specialized clinics and medical services that monitor and correct anticoagulant therapy for patients with appropriate indications. So Sullivan et al. in their work carried out an analysis of the economic efficiency of these specialized institutions[2]. The conclusion of their work, which assessed one state in the United States, was that the reduction in cost per patient across the state averaged $ 2,100 per year (based on 2004 prices), compared to the management of such patients in conventional hospital and clinical settings. Information about such studies has stimulated the further development of specialized anticoagulant therapy services (so-called anticoagulant clinics) in the United States. This demonstrates the cost-effectiveness of any personalization of warfarin treatment.

Currently, studies aimed at assessing the economic feasibility of further developing a personalized approach to dosing warfarin, which are based on the results of pharmacogenetic testing, are relevant. You et al. conducted a pharmacoeconomic analysis, which compared the economic efficiency of the pharmacogenetic approach to dosing warfarin over the traditional one[1,2]. The cost of therapy in the group not genotyped for CYP2C9 was US $ 155,700 versus US $ 150,500. The marginal cost of one additional major bleeding prevented was $ 5,778. The authors regard the result of their research as positive.

Conclusion

Currently, AKNDs are the only available drugs with the greatest proven efficacy in the prevention of thrombotic complications. The search for possible alternatives to AKND continues towards the creation of drugs from the group of direct thrombin inhibitors. High hopes were pinned on the direct oral thrombin inhibitor ximelagatran. Ximelagatran has shown positive results in clinical trials, and it was launched on the market in 2003 as an agent for the prevention of venous thromboembolism after orthopedic surgery, for the long-term prevention of recurrent venous thromboembolism after standard therapy, and for the prevention of strokes associated with a persistent

form of atrial fibrillation. But Ximelagatran has not been approved by the FDA for a variety of indications. Basically, due to the large number of cases of acute coronary syndromes in those taking this drug and the possibility of liver failure with long-term therapy (increased liver transaminases in 12% of cases)[1-5]. In February 2006, Astra Zeneca withdrew the drug from the market and discontinued its production. Currently, the only drugs from this group that are approved for use in many countries, incl. and in Russia, is argatroban, but its widespread use is limited by its high cost.

In the current circumstances, improving the quality of pharmacotherapy for AKND becomes a priority task both from the point of view of improving the quality and duration of patients' life, and in the economic aspect.

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