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Application of novel oral anticoagulants for the antithrombotic effect of cardiovascular system diseases

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Abstract: Long-term oral anticoagulant is one of the methods for the treatment of cardiovascular system diseases, and the most widely used anticoagulant drug is warfarin, but its clinical application has been greatly limited due to its slow onset, easy to affect by various factors, and difficult dose control. In recent years, with the continuous in-depth research on cardiovascular system diseases, the emergence of new oral anticoagulants (NOAC) has greatly impacted the status of traditional anticoagulant warfarin because of its safety, stability and convenience of consumption. The purpose of this article is to review the classification and application of novel oral anticoagulants.

Keywords: Warfarin; Novel Oral Anticoagulants; Anticoagulant Therapy; Cardiovascular Disease

Thromboembolic disease seriously threatens the life and health of patients, especially elderly patients, and has become the main cardiovascular disease faced by Chinese and Western countries. The use of anticoagulants is an indispensable step in the treatment of many cardiovascular diseases such as atherosclerosis, pulmonary embolism, atrial fibrillation and thrombosis.

1. Warfarin and novel oral anticoagulants

Warfarin, as a classic traditional anticoagulant drug, is often used clinically for the treatment of thromboembolism, but the drug has a slow onset, generally 3~4 days after medication, and the treatment window is narrow, the dose of medication varies greatly, and there is a risk of bleeding, so its clinical application is limited [1]. In recent years, through in-depth research on the coagulation mechanism in clinical practice, new oral anticoagulants (NOAC) are gradually replacing warfarin as the preferred drug for anticoagulation therapy.

2. Pharmacological characteristics of warfarin

Vitamin K as a procoagulant substance, has the effect of activating II., VII., IX., X. coagulation factors, warfarin structure is similar to vitamin K, can be used as a non-competitive inhibitor of vitamin K to inhibit vitamin K epoxide reductase, prevent its reduction to hydroquinone vitamin K, and then hinder the recycling of vitamin K in the body, thereby preventing the carboxylation of coagulation factors and coagulation proteins, producing anticoagulant effect [2], but has no effect on coagulation factors that have been carboxylated. Warfarin oral absorption in the gastrointestinal tract is fast and complete, mainly combined with albumin in the blood, plasma protein binding rate is about 99%, the apparent volume of distribution is very small, and the plasma half-life is about 40 hours. Warfarin is mainly metabolized by the liver, and its anticoagulant effect is easily affected by many factors, such as liver enzyme inhibitors can enhance its anticoagulant effect, liver enzyme inducers can inhibit its anticoagulant effect; Combined with drugs with high plasma protein binding rate can increase its anticoagulant effect, which is easy to cause bleeding; It can have a synergistic effect with antibacterial drugs, platelet inhibitors, etc. Although warfarin lasts for a long time, factors such as slow onset of action and difficult dose control may put patients at risk of bleeding or thrombosis, endangering life, health and safety.

3.Novel oral anticoagulants

(NOAC), i.e. non-vitamin K antagonists, including factor Xa inhibitors such as apixaban, rivaroxaban, edoxaban, and factor IIA inhibitors such as dabigatran. NOAC are increasingly used in anticoagulation therapy because of their good anticoagulant efficacy, low bleeding risk, predictable efficacy and safety, little genetic and drug interactions, and the need for routine testing of coagulation and dose adjustment [3].

3.1 Dabigatran ester

Dabigatran probiotic drug, dabigatran etexilate, is currently the only factor IIA inhibitor that can be used orally in clinical practice.

Dabigatran ester can be rapidly converted into dabigatran in the body after oral administration to exert its medicinal effect, which can directly inhibit free thrombin and thrombin that has been bound to fibrin, prevent fibrinogen from cleaving into fibrin, prevent coagulation from inducing platelet aggregation, and inhibit III., V., VII., X., XI. coagulation factors. The bioavailability of dabigatran etexilate is about 3%~7%, and the peak plasma concentration is reached after about 1~4h after oral administration, the plasma protein binding rate is about 35%, and the t1/2 is about 12~17h, without being metabolized by the liver drug enzyme CYP3A4. Dabigatran cilexetil biomass availability is low, about 6.5% [5], but the advantage of dabigatran etexilate is that it is not metabolized by the liver drug enzyme CYP450, so the interaction between food and drugs has less impact on it, and the drug is relatively safe [6], and does not cause liver damage.

3.2 Rivaroxaban

Rivaroxaban is the first oral factor Xa inhibitor, which reversibly inhibits factor Xa, which has inhibitory effects on both free and bound factor Xa, thereby inhibiting the conversion of fibrinogen to fibrin [6]. Rivaroxaban can reduce thrombin production, but has no effect on thrombin already produced, so it has little effect on physiologic hemostasis. Rivaroxaban has a rapid onset of action after oral administration, reaching the peak plasma concentration after about 2.5~4h, plasma protein binding rate is about 95%, T1/2 is about 5~9h, and elderly patients are about 11~13h. Rivaroxaban is mainly metabolized in the liver by the liver enzyme CYP3A4 and the liver enzyme CYP450, about 1/3 of the prototype drug is excreted by the kidney through urine, and about 2/3 is metabolized by the liver [7], of which 1/2 of the drug is excreted by the kidney, and the other 1/2 of the drug is excreted through the hepatobiliary route [8]. Experiments [9] have confirmed that rivaroxaban in patients with atrial fibrillation is not inferior to warfarin in preventing various types of stroke, and the safety is better.

3.3 Apixaban

Apixaban is similar to rivaroxaban, is a factor Xa inhibitor, pharmacokinetics and pharmacokinetics are also similar to rivaroxaban, highly selective for Xa coagulation factor, after oral administration about 1~4h after reaching the peak blood concentration, bioavailability is 60%, t1/2 is about 8~14h, plasma protein binding rate is 87%, about 24%-25% is excreted by the kidney, 75%~76% is metabolized by the liver enzyme CYP3A4. Apixaban can be eliminated by multiple metabolic excretion routes, including hepatic metabolism and renal excretion, so patients with mild impairment of liver and kidney function who cannot use other newer oral anticoagulants [10] can be treated with apixaban and are less likely to have a significant effect on their interactions with food and drugs. Apixaban should not be combined with liver enzyme CYP3A4 inhibitors and liver enzyme CYP450 inhibitors.

3.4 Edoxaban

Edoxaban is similar to rivaroxaban and apixaban, also a factor Xa inhibitor, pharmacokinetics and pharmacokinetics are also similar to the two, after oral administration about 1~2h to reach the peak blood concentration, bioavailability is 62%, t1/2 is about 9~10h, plasma protein binding rate is about 50%, about 35% is excreted by the kidneys, drugs entering the human body are rarely metabolized by the liver drug enzyme CYP450, only 4% are metabolized by the liver drug enzyme CYP450 [11]. The relatively low plasma protein binding rate is the more special of the three factor Xa inhibitors and may have implications for patients undergoing hemodialysis. Although edoxaban has certain advantages in the treatment of venous thromboembolism, studies [12] have shown that the probability of bleeding caused by orthopedic major surgery is slightly increased, so there is still controversy about whether edoxaban is suitable for the prevention of venous thromboembolism in orthopedic surgery. However, there are some limitations in this study, and the vast majority of patients in this study are Caucasian and racial differences with Chinese and Asian may cause imaccuracy in the results, so more rigorous randomized controlled trials are needed to further validate its safety.

4. Disadvantages and adverse reactions

Warfarin overdose can lead to vomiting, diarrhea and varying degrees of bleeding, when warfarin overdose, vitamin K antagonism can be given accordingly to inhibit the bleeding reaction of warfarin, if the bleeding is more serious, intravenous vitamin K, or fresh frozen plas-

ma, coagulation factor concentrate should be given to reverse the effect of warfarin. After the bleeding effect of warfarin has been suppressed, if it is necessary to continue warfarin, excessive use of vitamin K should be avoided to reduce resistance to warfarin.

Although dabigatran etexilate is better than warfarin in safety and efficacy, because most of it is excreted through the kidneys, long-term use of dabigatran etexilate will increase the burden on the kidneys, so the elderly and patients with renal insufficiency should consider the use of this drug as appropriate. Testing dabigatran etexilate is not available in most hospitals, and dabigatran etexilate can only be determined by calibrating diluted thrombin time (dTT) and viper venom clotting time (ECT) [13]. Dabigatran etexilate currently has no specific antagonists, and in the event of major bleeding, only prothrombin complex and fresh frozen blood can be relieved. In addition, dabigatran etexilate has a high price, which causes an economic burden for patients who take it for a long time, and the use should consider economic issues.

The half-life of rivaroxaban is short, its anticoagulant effect will be weakened after discontinuation, and its anticoagulant effect basically disappears after 16~24h, and patients need to be closely monitored to prevent excessive fluctuations in blood concentration from causing its anticoagulant effect to be unstable. Because rivaroxaban is mainly metabolized through the liver, it will increase the burden on the liver and affect the efficacy of the drug in patients with hepatic insufficiency.

The dose of apixaban needs to be combined with the patient's liver and kidney function, constitution, age and other factors to develop an appropriate plan, and patients with severe liver function are prohibited from using apixaban.

Only a small amount of edoxaban will be metabolized by CYP450, and the metabolic enzymes in the body have little effect on the metabolism of edoxaban, and the clinical use value is low.

5. Conclusion and outlook

Although the traditional oral anticoagulant warfarin has been used for decades, the efficacy has been clear, but there is still a narrow treatment window, its safety and efficacy are easily affected by the environment and the patient's own factors, and the food and drugs taken together are easy to affect its efficacy. With the clinical use, the insufficiency of warfarin has gradually affected the treatment of thrombosis and embolism. The emergence of new oral anticoagulants can make up for the shortcomings of warfarin to a certain extent, and its advantages are convenient to take, fixed dose, less interaction with food and drugs, higher bioavailability, wide treatment window, clear pharmacokinetics, small individual differences, stable effect, few complications, and can be used for long-term treatment. However, compared with warfarin, the higher price of new oral anticoagulants will bring financial burden to patients, and there is a lack of specific antagonists, and there is a lack of effective methods to reverse the anticoagulant effect of new oral anticoagulants when bleeding occurs. Looking back at the development of anticoagulant drugs, anticoagulant therapy has entered the post-warfarin era from the warfarin era, and the research and development of new drugs seems to be moving towards the goal of "safe, effective and controllable". With the expansion of clinical research, the application prospects of new oral anticoagulants will be more impressive. The era of anticoagulation represented by new oral anticoagulants is coming, although there are still some shortcomings in new oral anticoagulants, but with the further deepening of research, new oral anticoagulants will bring more benefits to patients, and I believe that there will be safer and more effective drugs and more rigorous treatment plans in the future, bringing good news to patients.

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