Research and Prospects of Anticoagulant Drugs: A Review

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Abstract. Anticoagulants prevent blood clotting by interfering with the body's physiological clotting process. Anticoagulants are mainly used to prevent the formation of blood clots and to stop the development of clots that have already formed. However, anticoagulants already in clinical use have many drawbacks. Conventional anticoagulants, which usually act on multiple coagulation factor targets, have proven efficacy in the prevention and treatment of thromboembolic disease. However, there are many inconveniences in clinical application. These inconveniences include slow onset of action, narrow therapeutic window and safe dosage range, high variability of the dose-effect relationship between individuals, susceptibility of blood levels to the effects of a variety of foods or medications, genetic and environmental factors affecting absorption and metabolism, and the need for frequent monitoring and dosage adjustments. Therefore, the development of new anticoagulants is imperative. The aim of this paper is to introduce traditional and novel anticoagulants and to provide an outlook on the future development of anticoagulants.

Keywords: Thrombin; Coagulation factors; Traditional anticoagulants; New Anticoagulant Drugs

1 Introduction

Anticoagulants are a class of drugs that prevent blood clotting by interfering with the body's physiological clotting process. This drug is used in the clinic primarily to prevent the formation of blood clots and to stop the further development of clots that have already formed. Heparin was the 1st anticoagulant to be discovered and isolated for medical use and is one of the oldest drugs still in clinical use, having been first used in humans in 1937. Warfarin was then first approved for medical use in 1954. By the late 1970s and early 1980s, low-molecular heparin appeared, opening up new avenues of anticoagulation therapy. In 1990, argatroban became available for clinical use. New oral anticoagulants dabigatran, rivaroxaban and apixaban have been marketed since 2004. From the overall development history, the development of anticoagulant drugs is a process of optimisation from indirect inhibition to direct inhibition, from multi-target to single-target, and from non-oral to oral. This paper summarises the development of

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traditional anticoagulants and new anticoagulants, aiming to tell the development lineage of anticoagulants and the outlook of future development for related research.

2 Segments of Action of Anticoagulants

The main link of action of anticoagulants is the targeting of prothrombin and coagulation factors.

2.1 Thrombin

Thrombin was first isolated from human serum in 1939 by American scientists such as Seeger, and began to be used in clinical practice[1].Thrombin is a multifunctional serine protease, which converted from inactive thromboplastin. It involved in the regulation of coagulation, anticoagulation, thrombosis and fibrinolysis. Under physiological conditions, prothrombin is mainly synthesised by the liver, and activation of the endogenous or exogenous coagulation cascade leads to the production of Xa, which cleaves prothrombin to form thrombin. Thrombospondin is a single polypeptide chain consisting of 582 amino acid residues. When thrombospondin is activated, two peptide bonds are broken, releasing a peptide containing 274 amino acid residues at the N-terminus. The remaining A and B chains are combined in a pair of disulphide bonds. There are several main reasons why anticoagulant drugs can target thrombin. First, thrombin is the key enzyme in the final common pathway that causes the clotting process. Second, thrombin-inhibiting drugs have yet to inhibit platelet aggregation. Third, heparin and low-molecular heparin inhibit only free thrombin, whereas direct thrombin inhibitors inhibit both fibrin-bound thrombin and free thrombin.

2.2 Blood Coagulation Factors

Blood coagulation factors are a series of important molecules involved in endogenous and exogenous blood clotting in the body. It and blood anti-coagulation factors (blood anti-coagulation factors) together constitute the body's coagulation system, maintaining the body's important physiological functions. When the body is affected by trauma and other factors that cause bleeding to occur, the activated coagulation factors will exert their anticoagulant effects through a series of physiological and biochemical processes to control bleeding[2].

For uniform nomenclature, the World Health Organisation uses Roman numerals to number the coagulation factors in the order in which they were discovered. Coagulation factors I, II, III, IV, V, VI, VII, VIII, IX, X, XI, D, XIII, etc. in that order. It has been found that coagulation factor VI is an activating factor. The coagulation factors excluding coagulation factor IV (calcium ion) are all proteins and most of the coagulation factors are synthesised by the liver.

Abnormalities in plasma coagulation factors can lead to an imbalance between coagulation and anticoagulation in the body. Therefore, inhibition of coagulation factors is an important direction in the development of anticoagulant drugs.

3 Traditional Anticoagulants

3.1 Heparin

In 1916, Jay McLean inadvertently discovered that liver extracts had strong anticoagulant activity in his experiments to find and purify pro-thrombotic substances in tissues. In 1918, William Howell and his student Emmett Holt improved the extraction method to obtain a purer anticoagulant, which they named "heparin"[3].Heparin, as a natural biomolecule, has a wide range of biological activities. The anticoagulant activity of heparin is one of its most widely used activities today. It can inactivate thrombin (activated factor II, activated factor X) due to its ability to bind to antithrombin. It neutralises activated coagulation factors IXa, Xa and XIa and inhibits thrombin generation, but it does not inactivate platelet-bound Xa. However, heparin is a mixture and its activity varies according to its constituents. Heparin binds to a variety of plasma and cellular proteins and has diverse pharmacokinetics; its bioavailability, half-life, and anticoagulant effect vary from person to person and require careful laboratory monitoring. In addition, side effects of heparin such as osteoporosis, which can induce thrombocytopenia, limit its use. Studies on heparin have found that the side effects of heparin are mainly related to its charge and relative molecular mass. Lowering its relative molecular mass decreases anti-IIa activity and attenuates inhibition of platelet aggregation, but enhances inhibition of coagulation factor Xa activity. Therefore, monitoring the intensity of anticoagulation with heparin is necessary. Ensure maximum anticoagulation effect while avoiding the risk of bleeding.

3.2 Low-Molecular Heparin

Low molecular weight heparin is a low relative molecular weight heparin fragment obtained by chemical or enzymatic depolymerisation of ordinary ungraded heparin or a low relative molecular weight heparin fraction obtained by a graded method. The basic structure of low-molecular heparin is a linear sulfated polysaccharide consisting of disaccharide repeating units (glucuronide GluA and glucosamine GlcN) linked by a 1,4-glycosidic bond. The hydroxyl group on GlcN may be sulphated, acetylated or present as an unprotected amino group. In 1987, natriuretic heparin was introduced as the first low molecular heparin. Immediately thereafter, more low molecular heparins were successfully developed. Compared with ordinary heparin, low molecular heparin has the advantages of low binding to plasma proteins, high bioavailability, long half-life, good absorption by subcutaneous injection, low incidence of adverse reactions, and no anticoagulation monitoring for clinical use[4]. However, the route of administration of low molecular heparin is mostly subcutaneous, which affects its use.

3.3 Hirudin

Haycraft was the first to discover the presence of anticoagulant substances in extracts of medical leeches in 1884. Jacoby named it hirudin in 1904. In 1955 Markwardt succeeded in isolating hirudin in pure form from the peripharyngeal glands of the medical

leech. Natural hirudin is an acidic single-chain polypeptide with a relative molecular mass of about 7000, consisting of 64-66 amino acids, containing three disulfide bonds and no polysaccharides. Seven isomers have been isolated and identified, which are highly active, structurally stable and not easily inactivated. Natural hirudin contains six cysteine residues with similar three-dimensional structure and distribution positions. The prothrombin active binding site is located at the N-terminus of its structurally compact (formed by disulfide bonds) (peptide 1-48). The thrombin fibrinogen binding site is then located at the C-terminus of its acid-rich amino acid residues (peptides 55-65). Amino acid residues in the intermediate region (peptides 49-54) then play a regulatory role. Natural hirudin has an extremely strong anticoagulant effect due to the special structure of its peptide chain[5]. However, hirudin binds irreversibly to thrombin and has no specific antagonist. And if hirudin is used in excess, it may aggravate the burden on the liver and kidneys and, in severe cases, may impair liver function, thus causing liver disease.

3.4 Aspirin

Aspirin was introduced in 1899 as an antipyretic and analgesic. As early as 1853, Charles Frédéric Gérard synthesised acetylsalicylic acid from salicylic acid and acetic anhydride, but failed to attract much attention. In 1898, the German chemist Feldhoffman synthesised it again and treated his father's rheumatoid arthritis with excellent results. It was introduced to the clinic in 1899 by Dreiser and named aspirin. Aspirin is an antiplatelet drug. It exerts its antiplatelet effect mainly by inhibiting arachidonic acid cyclooxygenase (COX), which leads to irreversible acetylation of Ser-529 and Ser-516, thus blocking TXA2 synthesis. However, long term use of aspirin medication can lead to problems with high blood clotting. Once a patient has suffered a cerebral haemorrhage, it is difficult to stop the bleeding and to prevent rebleeding after surgery. Long-term aspirin use therefore tends to increase postoperative risk in patients with cerebral haemorrhage[6].

4 New Anticoagulant Drugs

4.1 Dabigatran Etexilate

Dabigatran etexilate was first marketed in Germany and the UK in April 2008 by Boehringer Ingelheim. Dabigatran etexilate is a novel synthetic direct thrombin inhibitor, which belongs to the non-peptide class of thrombin inhibitors. It can directly inhibit prothrombin Ila factor in vivo, competitively binding to the specific binding site of fibrin, blocking the cleavage process of fibrinogen, thus preventing thrombosis and exerting its anticoagulant effect. Dabigatran etexilate is a new oral anticoagulant drug used primarily for the prevention and treatment of thromboembolism. It has the advantages of being a small molecule with a single target, safe and effective drug, fast drug onset after administration, and does not require constant drug monitoring. However, similar to the use and action of other anticoagulant drugs, dabigatran etexilate, as an anticoagulant, can cause bleeding when used in anticoagulant therapy. The rate of

haemorrhage is particularly high when applied in high doses[7]. Therefore its dosage needs to be very careful.

4.2 Rivaroxaban

Rivaroxaban is the world's first oral direct factor Xa inhibitor. It is highly selective and competitively inhibits free and bound factor Xa and prothrombin activity and prolongs activated partial thromboplastin time and prothrombin time in a dose-dependent manner. Rivaroxaban differs essentially from heparin in that it directly antagonises free and bound factor Xa reducing thrombin activation and thus prolonging clotting time. It not only has a blocking effect on the formation of blood clots, but also destroys clots that have already formed[8]. Rivaroxaban has the advantages of a high safety profile, efficacy, high oral bioavailability, and few food and drug interactions, eliminating the need for laboratory monitoring and dose adjustment. However, the use and dosage of rivaroxaban can vary greatly depending on the indication and the particular population.

4.3 Apixaban Tablets

Apixaban, which acts directly on coagulation factor Xa, was approved for marketing by the EU and the FDA in May 2011 and December 2012, respectively. It was launched in China in April 2013.Apixaban factor Xa inhibition is strong, even factor Xa bound to thrombus can be inhibited by apixaban, which then prevents thromboplastin from being activated into thrombin. Apixaban does not directly inhibit platelet aggregation and adhesion, but may do so indirectly by inhibiting thrombin activation and thus platelet aggregation. Compared to low molecular heparin, apixaban is administered orally at a more constant dose, which significantly improves patient compliance. However, this drug has not been on the market for a long time, and the experience of clinical application is still insufficient, so that apixaban still has certain risks in the indications, co-administration and other practical applications[9]. Therefore, caution needs to be taken with the medication. And apixaban is almost insoluble in water, the disadvantages of slow dissolution speed, low in vitro dissolution and low bioavailability have a certain impact on the absorption of the body. Therefore, in order to improve its bioavailability, increasing its dissolution rate is the key to research.

4.4 Agatheban

Argatroban is an arginine-derived small molecule peptide that reversibly binds only to prothrombin proteins and is a potent bivalent selective direct thrombin inhibitor, the world's first clinical anticoagulant to target only thrombin. The molecular weight of argatroban is 527U. Due to the small molecular weight of argatroban, it can enter into the inner part of the thrombus and simultaneously inactivate the thrombin bound to fibrin directly to dissolve the thrombus. As a new thrombin inhibitor synthesised in recent years, argatroban has the advantages of rapid onset of action, short duration of action, non-immunogenicity, and low risk of bleeding. However, there are limitations on the dosage and conditions for the use of argatroban in clinical applications because

of differences in the indications for argatroban formulations approved in various countries. There is still a risk of adverse effects such as haemorrhage, so there is a need to regulate the rational use of argatroban[10].

5 Conclusions

Conventional anticoagulants already in clinical use have many shortcomings. If regular and frequent check-ups are required, there is a high risk of bleeding, and there are many contraindications (many medications and even many foods can affect the anticoagulant effect of warfarin to varying degrees). Therefore the development of novel drugs is necessary. Currently new anticoagulants reduce the risk of bleeding but are more costly and reach a smaller audience. Future anticoagulants could combine several anticoagulants, both to reduce the risk of bleeding and to reduce costs, allowing anticoagulant efficacy to play a greater role. For example, low-dose aspirin combined with low-molecular heparin was effective in improving coagulation during pregnancy without significantly increasing the risk of bleeding[11], treatment of recurrent miscarriages in hypercoagulable states with low molecular heparin in combination with aspirin increases the rate of live births and improves patient coagulation. Future anticoagulants could combine several drugs or new anticoagulants could be developed. Eventually, anticoagulants will definitely move towards higher safety and lower cost.

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