Limitations of Traditional Anticoagulants

David Hawkins, Pharm.D.

Warfarin and unfractionated heparin have been in clinical use for more than 50 years. Both are effective anticoagulants, but their use is associated with a number of impediments, including the need for intensive coagulation monitoring, wide variation in dose-response relationships, multiple drug interactions (in the case of warfarin), and serious immune-mediated thrombocytopenia (in the case of heparin). The introduction of low-molecular-weight heparins 10 years ago advanced anticoagulation therapy by enhancing efficacy and eliminating the need for intensive coagulation monitoring. Fondaparinux, the first selective factor Xa inhibitor, represents yet another improvement in anticoagulation therapy with even greater efficacy and safety.
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Warfarin and unfractionated heparin (UFH) have been in clinical use as anticoagulants for more than 50 years. Both are highly effective when administered at proper dosages, and they are relatively safe when intensive anticoagulation monitoring and appropriate dosage adjustments are carried out efficiently. Compared with more recently developed anticoagulants, however, both warfarin and UFH are associated with a number of factors that complicate their clinical use.

The low-molecular-weight heparins (LMWHs) were introduced into clinical practice about 10 years ago. They represent an improvement over UFH because of a more predictable dose-response relationship and the fact that therapy with these smaller molecules of heparin does not require intensive laboratory monitoring.

Warfarin and the heparins interact with multiple targets within the coagulation cascade. Efforts to develop anticoagulants with a high degree of selectivity for a single target have led to the discovery of direct thrombin inhibitors and the factor Xa inhibitor fondaparinux. As explained in this article, these novel agents offer several advantages over the traditional anticoagulants.

From Mercer University Southern School of Pharmacy, Atlanta, Georgia.

Address reprint requests to David Hawkins, Pharm.D., Mercer University Southern School of Pharmacy, 3001 Mercer University Drive, Atlanta, GA 30341.

Warfarin

Warfarin is the only oral anticoagulant approved for the prevention and treatment of thromboembolism. Warfarin produces its anticoagulant effect by interfering with the hepatic synthesis of the vitamin K–dependent coagulation factors II, VII, IX, and X and the anticoagulant proteins C and S.[1] At therapeutic dosages, warfarin not only decreases the synthesis of coagulation factors by 30–50%, but it also reduces their biologic activity. Warfarin has no effect on circulating coagulation factors, and therefore its full anticoagulant effect is delayed for several days. Since circulating anticoagulant protein C is cleared more rapidly than most of the coagulation factors, a procoagulant condition exists transiently if warfarin therapy is started without the concomitant administration of an immediate-acting anticoagulant.

Another major limitation to the use of warfarin stems from its narrow therapeutic index. The anticoagulant response to warfarin is assessed by its effect on the international normalized ratio (INR), a value derived from the patient's plasma prothrombin time. The recommended therapeutic INR range for warfarin therapy in most conditions is 2.0–3.0.[2] An INR below 2.0 substantially increases the likelihood of thrombosis, and an INR above 3.0 is associated with an increased frequency of major bleeding.[3, 4] Maintaining a

patient's INR within the recommended therapeutic range requires frequent laboratory monitoring and appropriate adjustments in the dosage of warfarin. Even centers that have well-established anticoagulant clinics have a difficult time maintaining the INR within the therapeutic range. In one study, only 50% of INRs fell within the recommended range in an established anticoagulation clinic.[5]

The list of drugs that may interact with warfarin, causing either an increase or decrease in its anticoagulant activity, is long. Many herbal medicines (e.g., ginseng, garlic, Ginkgo bilboa) also have been reported to increase warfarin's activity and cause bleeding.[6] Certain foods high in vitamin K content, especially green leafy vegetables, also may attenuate or even eliminate the anticoagulant effect of warfarin. In addition to warfarin drug and food interactions, several disease states may alter the response to warfarin therapy. For example, cancer, collagen disease, heart failure, liver disease, and hyperthyroidism may increase warfarin's effects, whereas edema, hyperlipidemia, and hypothyroidism may decrease the anticoagulant response to warfarin.[2]

Resistance and increased sensitivity to warfarin may complicate dosage regimens. Hereditary warfarin resistance is a rare condition, but when present, may require warfarin dosages in excess of 20 mg/day to achieve a therapeutic INR.[7] Increased sensitivity to warfarin occurs more commonly, with approximately 10% of patients achieving therapeutic INRs while receiving warfarin 1.5 mg/day or even less. As many as 10–20% of Caucasians, but less than 5% of African-Americans or Asians, may possess one of several cytochrome P450 2C9 polymorphisms that result in a decreased conversion of warfarin to its inactive metabolite.[8]

Finally, warfarin is contraindicated in pregnancy because of teratogenicity and bleeding. Warfarin embryopathy may occur during the first trimester. Central nervous system abnormalities, fetal bleeding, and fetal death may occur throughout pregnancy.[1]

UFH and LMWHs

Unfractionated heparin is a heterogeneous mixture of polysaccharide polymers of varying molecular weight, ranging from 5000–30,000 daltons, with a mean molecular weight of 15,000 daltons. Chemical or enzymatic cleavage of the polysaccharide chains of UFH (a process called depolymerization) yields a mixture of heparin fractions with a mean molecular weight of approximately 5000 daltons, hence the term "low-molecular-weight heparins."

The anticoagulant activity of both UFH and the LMWHs is largely mediated through a distinct pentasaccharide sequence randomly distributed along the polysaccharide chains.[9] This sequence, which is found in only about one third of heparin molecules, binds heparin to the plasma protein antithrombin. Such binding causes a conformational change in antithrombin that markedly accelerates its inhibitory activity of activated factors Xa and XIIa. Unfractionated heparin and, to a lesser extent, LMWHs also inactivate thrombin by binding simultaneously to antithrombin and thrombin. Only heparin molecules with the distinct pentasaccharide sequence and at least 13 additional saccharide units are able to form the ternary complex composed of heparin, antithrombin, and thrombin. Compared with UFH, LMWHs have fewer polysaccharide chains of sufficient length to inactivate thrombin.

Because of differences in molecular size and anionic capacity, important differences exist in the bioavailability, plasma protein binding, dose-response relationships, and half-lives between UFH and LMWHs. The bioavailability of UFH administered subcutaneously is less than 30%. In contrast, subcutaneously administered LMWHs achieve a bioavailability in excess of 90%.[10] Unfractionated heparin binds more readily and extensively to plasma proteins and endothelial cells, which reduces its anticoagulant activity; this phenomenon explains the wide variation observed in UFH's dose-response relationship.[9] Because LMWHs bind less extensively to plasma proteins and endothelial cells, they produce a much more predictable and consistent anticoagulant response.

Heparins also bind to platelet factor 4, which neutralizes heparin's anticoagulant effect. Furthermore, the immune system may produce antibodies against the heparin–platelet factor 4 complex. In the presence of the heparin–platelet factor 4 complex, these antibodies can cause platelet activation and aggregation, thus leading to a paradoxical combination of low platelet count (thrombocytopenia) and a procoagulant state. This immune-mediated (type 2) heparin-induced thrombocytopenia (HIT) is associated with a 25–50% frequency of arterial and venous thromboembolic events and a 20–30% rate of mortality.[11] A milder non–immune-mediated form of thrombocytopenia (called type 1 HIT)

may occur during the first few days of heparin therapy but usually resolves even if heparin therapy continues. Type 1 HIT seldom causes clinical sequelae.

Type 2 HIT occurs in approximately 3% of patients receiving UFH and appears to occur less commonly in patients given LMWHs. However, there is almost 100% cross-reactivity between LMWH and antibodies from patients with type 2 HIT induced by UFH; therefore, LMWHs should not be used as an alternative anticoagulant in a patient with documented type 2 HIT.[12]

One of the major drawbacks to UFH for the treatment of thromboembolic disorders is the intensive coagulation monitoring required to achieve and maintain a therapeutic heparin level. Failure to reach the recommended activated partial thromboplastin time (aPTT) is associated with a marked increased frequency of thromboembolic events.[9] Several dosing nomograms have been developed in an attempt to reach the therapeutic aPTT rapidly, but even in the best of hands these methods sometimes fail.[13]

Another adverse effect that may attend long-term heparin therapy is osteoporosis.[14] Reduction in bone density and symptomatic vertebral fractures have been reported even in relatively young patients receiving heparin for 1 month or longer.[15] It is not exactly clear whether the risk of osteoporosis is lower in patients receiving long-term therapy with a LMWH. Clinical trials are under way to evaluate this question.

Novel Anticoagulants

Warfarin, UFH, and LMWHs act by inhibiting multiple targets within the coagulation cascade. Several new anticoagulants have been developed that specifically target a single coagulation protein. These new agents are classified as factor Xa inhibitors and direct thrombin inhibitors.

Fondaparinux sodium is the first selective factor Xa inhibitor that is in clinical use. It is a small, synthetic molecule that inhibits thrombin generation by selective catalytic enhancement of antithrombin-mediated factor Xa inhibition.[16] It has no effect on any other coagulation protein. Fondaparinux is a synthetic analog of the pentasaccharide sequence that binds heparin and LMWHs to antithrombin. Unlike the heparins, which are manufactured from animal tissue (usually porcine intestinal mucosa), fondaparinux is entirely synthetic.

Currently, there are three commercially available direct thrombin inhibitors—bivalirudin, argatroaban, and lepirudin; an oral direct thrombin inhibitor, ximelagatran, is in phase III of clinical development. Bivalirudin (in combination with aspirin) is used as an alternative to heparin in patients undergoing percutaneous coronary interventions. Argatroban and lepirudin are used in the treatment of HIT. Ximelagatran is being developed as a broad-spectrum anticoagulant. Unlike other anticoagulants, direct thrombin inhibitors inhibit thrombin without the assistance of cofactors. Another advantage of direct thrombin inhibitors is their ability to inhibit both circulating and fibrin-bound thrombin.

Unlike UFH and LMWHs, fondaparinux and the direct thrombin inhibitors do not bind to platelet factor 4 and therefore are not implicated as a cause of immune-mediated thrombocytopenia reminiscent of type 2 HIT. Even though the parenteral direct thrombin inhibitors require coagulation monitoring, fondaparinux and ximelagatran apparently do not. Unlike warfarin, both fondaparinux and all the direct thrombin inhibitors produce an immediate anticoagulant effect. There are no known drug interactions associated with these new compounds.

Conclusion

Traditional anticoagulants, although highly effective, are fraught with difficulties including unpredictable dose-response relationships, a narrow therapeutic index, the need for intensive laboratory monitoring, life-threatening adverse effects, and, in the case of warfarin, a multitude of potential drug interactions. Some of the more recently developed anticoagulants have a predictable dose response, do not require coagulation monitoring, do not cause HIT, and are relatively safe to use in combination with other drugs.

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