Advances in the Treatment and Prevention of Venous Thromboembolism

The New World After Heparin

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ABSTRACT

Venous thromboembolism (VTE) is a common condition and a source of significant morbidity and mortality. Traditional agents for the treatment and prevention of VTE include unfractionated heparin, low molecular weight heparin, and vitamin K antagonists. The limitations of these compounds, including narrow therapeutic windows, contamination by impurities, variable dose responses, lack of oral bioavailability, and need for laboratory monitoring, have created the need for newer anticoagulants. Current efforts are focused on the development of new classes of drugs that target specific steps in the coagulation cascade. These new drugs include direct and indirect inhibitors of activated Factor X, direct thrombin inhibitors, and novel anticoagulants. These new drugs are characterized by favorable pharmacologic profiles, dosing convenience, lack of immunogenicity, and efficacy and safety profiles at least as favorable as those of conventional anticoagulants.

INTRODUCTION

Venous thromboembolism (VTE) is a common and complex vascular disorder with a multifactorial pathogenesis.[1] The primary pathogenetic factors that contribute to VTE are venous stasis, injury to the venous endothelium, and a hypercoagulable state. The risk of VTE may be increased by hospitalization, malignancy, immobilization, surgery, venous trauma, and pregnancy. Hereditary risk factors include the factor V Leiden mutation, the G20210A prothrombin gene mutation, and deficiencies of protein C, protein S, and antithrombin. Thrombophilia is a relatively new term applied to patients with recurrent venous or arterial thrombosis from inherited or acquired causes. Acquired thrombophilias include anticardiolipin antibodies, lupus anticoagulant, and increased levels of coagulation proteins.

The most common clinical manifestation of VTE is deep venous thrombosis (DVT), which usually arises in the deep veins of the calf and spreads upward. Pulmonary embolism (PE), a more serious manifestation, occurs as a complication of DVT proximal to the deep calf veins.

The annual incidence of diagnosed VTE is 1 to 2 events per 1000 persons in the general population.[2] More than 250,000 patients are hospitalized annually with VTE in the United States, some of whom die from pulmonary emboli and many of whom develop recurrent pulmonary VTE within ten years. The incidence of VTE is similar in men and women, but it is more common in Caucasians and African-Americans than in Hispanics and Asians.

The cornerstone of treatment and prevention is anticoagulant therapy.[3] Traditional anticoagulants include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and the oral vitamin K antagonist, warfarin. UFH is usually given by constant intravenous infusion and is therefore complicated to administer. The clearance of UFH is rapid and dose-dependent, and its kinetics unpredictable. Heparin-induced thrombocytopenia (HIT) develops in 3-4% of patients who receive UFH for at least 7-10 days. Heparin-induced osteopenia (bone demineralization) may occur when UFH is administered for over 1 month, apparently due to elevation of parathyroid hormone.

The production of heparin begins with the intestines of pigs. Recently, there have been several reports of severe allergic reactions and deaths as a result of impurities that entered the final product during the manufacturing process.

LMWH was the first class of new anticoagulants to become widely available as alternatives to UFH.[4] They are fractionated from the parent molecules to create compounds with mean molecular weights of approximately 4 kD (kiloDalton). Despite their small size, LMWHs have longer effective plasma half-lives than UFH, and because of their favorable dose-response characteristics, monitoring is unnecessary in most patients. LMWH is typically dosed subcutaneously and is much less likely to cause HIT or osteopenia. LMWHs are frequently used for inpatient and OPD therapy. Currently in the U.S., LMWH is mostly used for prophylaxis, since the need

for parenteral administration complicates long-term use in outpatient settings.

Warfarin remains the most commonly used option for the long-term outpatient treatment of VTE. It is usually started with, or soon after the beginning of, UFH therapy. As is well known, Warfarin has an unpredictable pharmacokinetic profile and a variable dose-response relationship, and it requires frequent monitoring and dose adjustments to maintain a target anticoagulation intensity that is both safe and effective. Diet, co-morbidities, and numerous drugs interact with warfarin so that careful monitoring is necessary.

Novel antithrombotic agents, with more specific activities in the coagulation cascade, more predictable pharmacodynamics and pharmacokinetics, simpler dosing regimens, and few or no laboratory monitoring requirements, have been developed to overcome limitations associated with some of the nonspecific traditional anticoagulants. For the acute treatment and extended secondary prevention of VTE, evidence is emerging to support the use of drugs that inhibit activated Factor X (Factor Xa), or oral drugs that directly inhibit thrombin.[5,6] Other novel anticoagulant agents are in various stages of clinical development.

INHIBITION OF FACTOR Xa (ACTIVATED FACTOR X)

Thrombin generation occurs by two pathways: the *extrinsic* pathway is the major physiologic pathway for initiating formation of fibrin, and the *intrinsic* pathway is considered important for fibrin maintenance and propagation. Factor X has a central role in thrombin generation based on its position at the start of the common pathway of the extrinsic and intrinsic coagulation systems, which means it can be activated by either pathway.

Discovered in 1956, Factor X, or Stuart-Prower factor, was first identified in a Ms. Audrey Prower of London, who had a lifelong bleeding tendency.

Once it has been activated, Factor Xa becomes an essential component of the prothrombinase complex. Since assembly of the prothrombinase complex represents the second to last step in thrombin generation, interference with Factor Xa activity directly affects the amount of active thrombin generated and, therefore, the amount of fibrin formed. Preclinical and clinical data support the concept that inhibition of Factor Xa can control thrombogenesis, and this finding has stimulated the development of indirect and direct Factor Xa-inhibiting agents (Table 1).

TABLE 1. FACTOR Xa-INHIBITING AGENTS.

Indirect	
	fondaparinux
	idraparinux
Direct	
	razaxaban
	apixaban
	rivaroxaban

INDIRECT FACTOR Xa INHIBITORS

Fondaparinux

Fondaparinux is the first in a new class of antithrombotic agents, the selective indirect Factor Xa inhibitors.[7] Recall that heparin's main anticoagulant effect depends upon a pentasaccharide sequence in its molecule that binds to antithrombin and potentiates its inhibition of Factor Xa. (AT, formerly called antithrombin III, is the primary endogenous inhibitor of the coagulation cascade) Fondaparinux was developed as a synthetic analog of heparin's antithrombin-binding pentasaccharide sequence. It too is a catalyst for AT, resulting in an approximate 300-fold acceleration in its basal rate of Factor Xa inactivation with no effect on its basal rate of thrombin inactivation.

Fondaparinux is a small, synthetically produced molecule and preparations are consistent from batch to batch. Bioavailability is nearly complete after subcutaneous injection, onset of antithrombotic activity is rapid, and the peak plasma level is reached in about 2 hours. Elimination is exclusively renal, with a half-life of about 17 hours that is dose-independent, allowing once-daily dosing. The reproducible and linear pharmacokinetic profile exhibits minimal variation among patients or doses, which makes dose adjustment and hemostatic monitoring mostly unnecessary except in patients with renal insufficiency.

Fondaparinux does not interact with protamine sulfate, the antidote for UFH, so in the unlikely event that uncontrolled bleeding occurs, treatment with a procoagulant such as recombinant factor VIIa may be effective. HIT is also unlikely with fondaparinux because the drug does not induce the formation of heparin/PF4 complexes that serve as the antigenic target for the antibodies that cause HIT.[8]

Prophylaxis of VTE. Treatment with fondaparinux may further reduce the risk of VTE following orthopedic surgery compared with enoxaparin, a LMWH. A recent meta-analysis of 4 multicenter, randomized, double-blind trials in 7344 patients undergoing elective hip replacement, elective major knee surgery, and surgery for hip fracture, found that in comparison with enoxaparin, fondaparinux significantly reduced the incidence of VTE by postoperative day 11 from 13.7% to 6.8% ($P < .001$), a 50% reduction.[9] Major bleeding occurred more frequently with fondaparinux ($P = .008$), but the incidence of clinically relevant bleeding was similar in both groups.

Extended prophylaxis with fondaparinux decreased the risk of VTE by 96% in a double-blind, multicenter study of 656 patients undergoing hip fracture surgery who were randomized to receive fondaparinux or placebo for 19 to 23 days after completing the initial prophylaxis treatment of seven to ten days using fondaparinux.[10] The incidence of VTE compared with placebo was reduced from 35.0% to 1.4% ($P < .001$). The incidence of clinically relevant bleeding was similar in both groups.

Postoperative fondaparinux was at least as effective as perioperative treatment with the LMWH dalteparin in a double-blind study of 2048 patients undergoing major abdominal surgery.[11] The rate of VTE was 6.1% with dalteparin and 4.6% with fondaparinux, a relative risk reduction of 24.6% ($P = 0.144$), which met the predetermined study criterion for non-inferiority of fondaparinux. Major bleeding was observed in 3.4% of the fondaparinux group and 2.4% of the dalteparin group ($P = 0.122$).

Fondaparinux is effective in the prevention of VTE in older acute medical patients, according to a double-blind study of 849 medical patients aged 60 years and above who were randomized to receive placebo or 2.5 mg fondaparinux subcutaneously once daily for six to 14 days.[12] VTE was detected in 10.5% of the placebo group and 5.6% of the fondaparinux group, a relative risk reduction of almost 50%.

Treatment of VTE. Once-daily fondaparinux is at least as effective and as safe as adjusted-dose UFH in the initial treatment of hemodynamically stable patients with PE. This finding is based on an open-label study of 2213 patients with acute symptomatic PE who were randomized to receive either fondaparinux subcutaneously once daily without monitoring or a continuous intravenous infusion of UFH, both given for at least 5 days and until the INR became therapeutic with warfarin.[13] Recurrent thromboembolic events occurred in 5.0% of the UFH patients and 3.8% of the fondaparinux patients, an absolute reduction of 1.2%. Major bleeding occurred in 1.1% and 1.3% of the UFH and fondaparinux groups respectively. Mortality rates at 3 months were similar in both groups. In the fondaparinux group, 14.5% of patients received the drug partly as outpatients.

Fondaparinux proved at least as effective and safe as the LMWH enoxaparin in a randomized, double-blind study of 2205 patients with symptomatic DVT.[14] Fondaparinux, 7.5 mg (adjusted to 5.0 mg in patients weighing <50 kg and 10.0 mg in patients weighing >100 kg) was administered subcutaneously once daily, and enoxaparin, 1 mg/kg of body weight, was administered subcutaneously twice daily for at least 5 days. Recurrent thrombolic events occurred in 4.1% of the enoxaparin patients and 3.9% of the fondaparinux patients, an absolute reduction of 0.15% (without rounding). Major bleeding occurred in 1.2% of those receiving enoxaparin and 1.1% of patients receiving fondaparinux. Mortality rates were 3.0% and 3.8% in the enoxaparin and fondaparinux groups, respectively.

Safety in heparin-induced thrombocytopenia (HIT). HIT is a potentially serious complication of heparin treatment. Type I HIT is a benign, non-immune mediated, temporary decrease in platelet levels after heparin administration. Type II HIT is an immune-mediated reaction which can cause thrombosis leading to limb gangrene or even death. HIT type II is mediated by an IgG antibody to the heparin–platelet factor 4 (PF4) complex, and usually develops 5 to 10 days after heparin treatment is started, but can become manifest earlier in patients with previous exposure to heparin. The antibody–heparin–PF4 complex binds to platelet surface receptors and induces platelet activation and aggregation, and simultaneously, activates blood coagulation pathways and endothelial tissue factor.

Successful use of fondaparinux has been reported anecdotally in patients with a history of HIT during LMWH administration, although the drug is not currently approved for these indications.[15]

Acute coronary syndromes. In patients with acute coronary syndromes, fondaparinux has proven similar to enoxaparin in reducing the risk of ischemic events at nine days, but superior to enoxaparin in decreasing episodes of major bleeding and long term morbidity and mortality. A group of 20,078 patients with acute coronary syndromes were randomized to receive either fondaparinux (2.5 mg daily) or enoxaparin (1 mg per kilogram of body weight twice daily) for a mean of six days.[16] The primary outcome was death, myocardial infarction, or refractory ischemia at nine days. The number of patients with primary-outcome events was similar in the fondaparinux and enoxaparin groups (5.8% and 5.7%, respectively). The rate of major bleeding at nine days was significantly lower with fondaparinux than with enoxaparin (2.2% vs. 4.1%; P < .001), as was mortality at 30 days (P = .02) and at 180 days (P = .05).

Idraparinux

Idraparinux is a methylated and therefore long-acting congener of fondaparinux with the same mechanism of action. As another synthetic analogue of the pentasaccharide sequence in heparin, it also works by catalyzing AT's inhibition of Factor Xa, but methylation raises its binding affinity considerably. Idraparinux is administered once a week by subcutaneous injection, resulting in stable therapeutic anticoagulant levels without the need for monitoring.

Treatment of DVT and PE. The efficacy and safety of idraparinux versus standard therapy were examined in 2 randomized, open-label noninferiority trials involving 2904 patients with DVT and 2215 patients with PE.[17] Patients received either subcutaneous idraparinux (2.5 mg once weekly) or heparin followed by an adjusted-dose vitamin K antagonist for either 3 or 6 months. In the study of patients with DVT, the incidence of recurrence at day 92 was 2.9% in the idraparinux group and 3.0% in the standard therapy group, a result that satisfied the prespecified noninferiority requirement. The rates of clinically relevant bleeding at day 92 were 4.5% in the idraparinux group and 7.0% in the standard therapy group (P = .004). In the study of patients with PE, the incidence of recurrence at day 92 was 3.4% in the idraparinux group and 1.6% in the standard therapy group (odds ratio, 2.14), a finding that did not meet the noninferiority requirement.

Prophylaxis of VTE. Idraparinux is more effective than placebo in preventing recurrent VTE but is associated with a higher risk of major bleeding. A group of 1,215 patients with DVT or PE who had completed 6 months of therapy with idraparinux or a vitamin K antagonist and in whom extended anticoagulation was warranted, were randomized to receive once-weekly injections of 2.5 mg of idraparinux or placebo for 6 months without monitoring.[18] Recurrent VTE occurred in 1.0% of the idraparinux group and 3.7% of the placebo group (P = .002). Major bleeding occurred in 1.9% of the idraparinux group and in none in the placebo group (P < .001).

DIRECT FACTOR Xa INHIBITORS

Direct factor Xa inhibitors bind directly to the active site of Factor Xa, thereby blocking its interaction with its substrates.[8] These drugs inhibit both free Factor Xa and Factor Xa bound to activated platelets within the prothrombinase complex. This property may confer a therapeutic advantage compared with UFH, LMWR, and the indirect Factor Xa inhibitors. Direct Factor Xa inhibitors appear to inhibit thrombus formation while allowing sufficient thrombin to be generated to activate platelets, thereby maintaining the ability of form a hemostatic plug. As a result, these agents may have a lower bleeding potential than conventional anticoagulants.

Razaxaban

Razaxaban is a highly potent, selective, and orally bioavailable direct Factor Xa inhibitor. Razaxaban was compared with enoxaparin 30 mg twice daily in a phase 2 dose-finding study in 656 patients who underwent elective knee arthroplasty.[19] At doses of 25, 50, 75, and 100 mg twice daily, both efficacy and safety were dose related. The lowest razaxaban dose trended toward greater effectiveness than enoxaparin, with similar low rates of major bleeding. Treatment with the 3 higher doses of razaxaban was stopped prematurely because of excessive major bleeding.

Apixaban

Apixaban exhibits a high degree of potency and selectivity toward Factor Xa and has an improved pharmacokinetic profile relative to razaxaban. In a dose-finding study, the investigators concluded that apixaban can be administered in a fixed dose as a sole treatment and

appears to be an attractive alternative to standard therapy in patients with DVT. 520 patients with acute symptomatic DVT were randomized to receive apixaban 5 or 10 mg twice daily, apixaban 20 mg once daily, LMWH, or fondaparinux followed by an open-label vitamin K antagonist for 84-91 days.[20] The primary efficacy outcome was the composite of symptomatic recurrent VTE and deterioration of the thrombotic burden as assessed by ultrasonography and perfusion lung scanning. The primary safety outcome was the composite of major and clinically relevant non-major bleeding. For apixaban 5 and 10 mg twice daily and 20 mg once daily and for vitamin K antagonist, the primary efficacy outcome rates were 6.0%, 5.6%, 2.6%, and 4.2%, respectively, and the primary safety outcome rates were 8.6%, 4.5%, 7.3%, and 7.9%, respectively.

Rivaroxaban

Rivaroxaban is a once-daily, oral, direct Factor Xa inhibitor in advanced clinical development for the prevention and treatment of VTE. The pharmacokinetic and pharmacodynamic properties of rivaroxaban are predictable after once- and twice-daily dosing, and the effects of age, renal function, and body weight on rivaroxaban distribution and clearance are minimal.[21]

Prophylaxis after total hip arthroplasty. Rivaroxaban is significantly more effective than enoxaparin for extended thromboprophylaxis after total hip arthroplasty and has a similar safety profile, according to a study of 4541 patients randomized to receive oral rivaroxaban or subcutaneous enoxaparin for a mean of 35 days following total hip arthroplasty.[22] Overall, compared with enoxaparin prophylaxis, rivaroxaban was associated with a risk reduction of 70% ($P < .001$) in the composite endpoint of any DVT, non-fatal PE, and all-cause mortality, and a reduction of 88% ($P < .001$) in major VTE. The incidence of major and non-major bleeding was similar in both groups.

Compared with short-term enoxaparin (10-14 days, followed by placebo), extended duration rivaroxaban (mean 35 days) was associated with a risk reduction of 79% ($P < .001$) in the composite endpoint of any DVT, non-fatal PE, and all-cause mortality, and 88% ($P < .001$) for major VTE in 2509 patients undergoing total hip arthroplasty.[23] Safety outcomes were similar in both groups.

Prophylaxis after total knee replacement. In a double-blind trial of 2531 patients undergoing total knee replacement, rivaroxaban resulted in a resource use savings of $192 per patient due to improved health outcomes relative to enoxaparin.[24] Patients were randomized to receive rivaroxaban 10 mg or enoxaparin 40 mg once daily for 10 to 14 days.[25] Rivaroxaban yielded a relative risk reduction of 49% ($P < .001$) in the primary efficacy endpoint (VTE diagnosed by mandatory venography, symptomatic VTE, and all-cause mortality), and 62% ($P = .01$) in the major secondary efficacy endpoint (proximal DVT and PE and VTE-related death). In the rivaroxaban and enoxaparin groups, rates of major bleeding were 0.6% and 0.5%, and rates of any bleeding were 4.9 and 4.8%, respectively.

Treatment of DVT. Rivaroxaban administered once- or twice-daily is as safe and effective as standard therapy for the treatment of acute symptomatic DVT, according to an analysis of data from 2 separate phase II studies with a total of 1156 patients.[26] Thrombus regression at 3 weeks was greater with twice-daily than once-daily rivaroxaban dosing, although a comparison of bleeding rates at 3 months favored once-daily dosing.

Safety in HIT. Rivaroxaban does not activate HIT antibodies and can be used in patients with HIT without risks of adverse side effects. In an analysis of sera from 89 patients with a total of 152 different HIT antibody/donor platelet combinations, rivaroxaban showed no cross-reactivity with any HIT antibodies and did not promote the release of PF4 from platelets as did UFH and LMHW.[27]

DIRECT THROMBIN INHIBITORS

Direct thrombin inhibitors (DTIs) are a new class of anticoagulants that bind directly to thrombin and block its interaction with its substrates.[28] DTIs have several potential advantages over indirect thrombin inhibitors such as UFH and LMWH. Because they exhibit minimal binding to plasma protein, their response to anticoagulation is predictable. Unlike heparin, and like the synthetic antithrombin activators, they do not bind platelet factor 4 (PF4) or crossreact with autoantibodies that cause HIT. The potential for drug-drug interactions with DTIs appears low, and DTIs do not have the same problems with food interactions as warfarin. The therapeutic window of some DTIs is sufficiently broad that routine monitoring and dose adjustment are unnecessary. The main disadvantages of DTIs are the lack of an antidote or readily available clinical monitoring.

Lepirudin

Hirudin is a protein with anticoagulant properties originally extracted from the salivary gland of the medicinal leech, *Hirudo medicinalis*. Lepirudin is a recombinant hirudin and the first DTI approved by the FDA (in 1998) for prophylactic use in patients with HIT. It's predominant route of elimination is via renal excretion. Lepirudin has been primarily evaluated in patients with acute coronary syndromes including unstable angina and myocardial infarction, and in cardiac surgery for patients with HIT.

In a study of 82 patients with acute HIT who received 1 of 4 intravenous lepirudin regimens during cardiopulmonary bypass, platelet counts increased rapidly in 89% of patients.[29] The incidence of the combined end point (death, amputation, new VTE complications) was significantly reduced in lepirudin-treated patients compared with historical controls (P = .014). Bleeding rates were similar in both groups. An analysis of three combined trials (403 patients) revealed that, compared with the historical control group, lepirudin reduced the combined endpoint significantly (30% vs 52%; P = .05).[30] Major bleeding was more frequent in the lepirudin-treated patients (29% vs 9%, P = .01) which may reflect the need for a smaller starting dosage.

It is important to monitor the PTT and adjust dosages accordingly, and wait until the platelet count approaches normal, before correcting the patient to warfarin.

Bivalirudin

Bivalirudin is a synthetic analog of hirudin that inhibits thrombin directly by binding simultaneously to its active catalytic site and its substrate recognition site. Bivalirudin rapidly induces anticoagulation, has a relatively short duration of action, and displays linear kinetics. Bivalirudin decreases both ischemic and bleeding complications associated with percutaneous coronary intervention (PCI) and may be useful in patients with unstable angina not undergoing PCI and in those with MI receiving thrombolytic therapy with streptokinase.

In 13,819 patients with acute coronary syndromes, bivalirudin plus a glycoprotein IIb/IIIa inhibitor, as compared with heparin plus a glycoprotein IIb/IIIa inhibitor, was associated with noninferior 30-day rates of the composite ischemia end point of death, MI, or unplanned revascularization (7.7% and 7.3%), major bleeding (5.3% and 5.7%), and the net clinical outcome end point defined as the combination of composite ischemia or major bleeding (11.8% and 11.7%).[31] Bivalirudin alone, as compared with heparin plus a glycoprotein IIb/IIIa inhibitor, was associated with a noninferior rate of the composite ischemia end point (7.8% and 7.3%) and significantly reduced rates of major bleeding (3.0% vs. 5.7%; P < .001) and the net clinical outcome end point (10.1% vs. 11.7%; P = .02).

Argatroban

Argatroban is a DTI derived from l-arginine that binds rapidly and reversibly to both circulating and clot-bound thrombin. The relatively short elimination half-life of argatroban (39 to 51 minutes), and its reversible binding, allow rapid achievement of therapeutic effect and rapid restoration of normal hemostasis upon cessation of therapy. Argatroban produces a predictable dose response, and its anticoagulant activity can be monitored with routine coagulation tests.

In a study of 418 patients with HIT or HIT with thrombosis (HITT), intravenous argatroban therapy significantly reduced the composite endpoint compared with historical controls. All-cause death, all-cause amputation, or new thrombosis in 37 days occurred in 28% of patients treated with argatroban vs 39% of controls; P = .04. In the HITT arm, the composite end point was reduced to 42% by argatroban, compared with 57% of controls (P = .07). Platelet counts recovered more rapidly in argatroban-treated patients, and bleeding rates were similar in both groups.[32]

Argatroban is the drug of choice in patients with renal insufficiency where lepirudin is contraindicated.

Dabigatran

Dabigatran is a low-molecular-weight DTI that binds to thrombin with high affinity and specificity and which can be administered orally as the prodrug dabigatran etexilate. Dabigatran etexilate demonstrates an acceptable safety profile across a wide range of doses, and the therapeutic window appears to be between 12.5 mg and below 300 mg twice daily.

In a multicenter, parallel-group, double-blind study, 1973 patients undergoing total hip or knee replacement were randomized to 6-10 days of oral dabigatran etexilate or subcutaneous enoxaparin starting 12 hours prior to surgery.[33] The primary efficacy parameter was the incidence of VTE, and a significant dose-dependent decrease in VTE occurred with increasing doses of dabigatran etexilate (P < .0001). Compared with enoxaparin, VTE was

significantly lower in patients receiving dabigatran 150 mg twice daily (odds ratio [OR] 0.65; P = 0.04), 300 mg once daily (OR 0.61; P = .02) and 225 mg twice daily (OR 0.47, P = .0007). Compared with enoxaparin, major bleeding was significantly lower with dabigatran 50 mg twice daily (0.3% vs 2.0%; P = .047) but increased with higher doses. For extended prophylaxis of VTE after total hip replacement surgery, oral dabigatran administered once daily for a median of 33 days was as effective as enoxaparin and had a similar safety profile.[34] There was no evidence of hepatic toxicity, which limited the development of ximelagatran, another effective DTI.

NOVEL ANTITHROMBOTIC AGENTS

Novel antithrombotic agents, with more specific activity in the coagulation cascade, more predictable pharmacodynamics and pharmacokinetics, simpler dosing regimens, and few or no laboratory monitoring requirements, are in various stages of development with the goal of overcoming the limitations associated with some of the nonspecific traditional anticoagulants.

Recombinant Nematode Anticoagulant Protein

Recombinant nematode anticoagulant protein c2 (rNAPc2) is a potent inhibitor of the tissue factor/factor VIIa complex that has the potential to reduce ischemic complications mediated by thrombin generation. An open-label, sequential dose-ranging study was performed in 293 patients to determine a safe and effective dose of rNAPc2 for prevention of VTE after elective, unilateral total knee replacement.[35] A dosage of 3.0 mcg/kg administered subcutaneously within 1 hour after surgery provided the best observed results, with an overall DVT rate of 12.2%, a proximal DVT rate of 1.3%, and a major bleeding rate of 2.3%. Treatment with rNAPc2, at doses up to 7.5 mcg/kg, in combination with aspirin, clopidogrel, and UFH appears to be a safe and effective strategy to prevent thrombin generation during coronary angioplasty.[36]

Oral Low Molecular Weight Heparins

LMWHs exhibit limited oral absorption and usually have to be administered parenterally. In an effort to increase the oral bioavailability of LMWH, various strategies have been developed including chemical conjugation with carrier molecules, microemulsification, and encapsulation into nanoparticles.[37] Several of these experimental compounds have shown promise in animal studies and may become candidates for development in human clinical trials.

CONCLUSIONS

Heparin and coumarin derivatives have long been used for the prophylaxis and treatment of VTE. Although these agents are clinically effective and relatively safe because of the vast experience with their use, they act at multiple targets within the coagulation cascade and their efficacy is influenced by multiple variables.

Heparin remains the standard drug for DVT prophylaxis in patients undergoing abdominal or pelvic surgery and for high risk medical patients. However, the recent upsurge in allergic complications from impurities in the manufacture of this biologic product, heightens the appeal of the more expensive but purer synthetic drugs.

Because of the need to improve the benefit-to-risk ratio of antithrombotic drugs, newer agents that target individual coagulation factors have been developed. The advantages of these newer agents include favorable pharmacologic properties, relative safety and efficacy as compared with established treatments, ease of administration, and lack of immunogenicity. The relatively higher costs of these newer compounds remains a drawback, but these costs may be offset, in part, by improvements in clinical outcomes. Additional studies are needed to identify the optimal roles and future potential of these newer anticoagulants.

Vena cava filters are being used more frequently for the prophylaxis and therapy of DVT. Their use in patients who have a high potential for bleeding or who progressed while therapeutically anticoagulated is based on sound evidence, but their use in patients who could be well served by one of the many available drugs is problematic and should not be encouraged.

Many of the less familiar drugs described in this report are currently available or may be approved in the near future, and merit strong consideration for use.

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