Despite the chemical arsenal available for thrombosis prevention, unfractionated heparin (UFH), and low-molecular-weight heparins (LMWHs), clot remains a major threat for medical and surgical patients. In the absence of prophyllaxis, venous thromboembolism (VTE) occurs in 10% to 40% of medical and general surgery patients and in 40% to 60% of major orthopedic patients. Heparin was discovered by chance 60 years ago from the extracts of dog livers. For 40 years, heparin was the mainstay for parenteral anticoagulation, although the mechanisms of action were not clearly understood. Low-molecular-weight heparins were also found by chance in the late 1970s and were in clinical use nearly a decade before the benefits of use was discovered. Now, a new class of parenteral anticoagulants, pentasaccharides, offers clinicians another pathway to modulate the coagulation cascade to prevent clot.

**PATHOPHYSIOLOGY OF CLOT**

Thrombosis in arterial circulation is usually related to disruption of the endothelial lining of vessel walls, particularly in areas of atheroma. The resulting exposure of subendothelial tissue results in formation of platelet plugs or white thrombus. The atheroma and platelets express tissue factor, which activates the coagulation pathway. Because of the major role platelets play in the formation of white thrombi, antiplatelet agents are the preferred choice to prevent arterial thrombi.

In the venous tree and cardiac atria, red thrombus can result from blood stasis and activation of the coagulation cascade with entrapment of erythrocytes. Anticoagulants are the preferred choice to prevent venous thrombosis. Unfractionated heparin and LMWHs must be administered parenterally and share in the risky side effects of heparin-induced thrombocytopenia (HIT) and osteoporosis with long-term use. Unfractionated heparin requires regular laboratory tests for monitoring.

**A COMPARISON OF PARENTERAL AGENTS**

After entering the bloodstream via intravenous or subcutaneous (SC) route, UFH binds to a variety of plasma proteins including glycoprotein platelet factor 4, vitronectin, and von Willebrand, which lowers bioavailability and produces a variable anticoagulant response. Unfractionated heparin inhibits multiple factors in the coagulation cascade particularly factor IIa or thrombin. Receptor-mediated uptake by endothelial cells and macrophages with renal activity clears heparin from the plasma. As a result, drug effects are not linearly related to dose in a therapeutic range. For example, the half-life of 25 U/kg of heparin is 30 minutes, whereas a dose of 400 U/kg is 150 minutes. In patients requiring reversal, protamine can rapidly and completely neutralize UFH, which makes this agent perfect for coronary bypass surgery. Unfractionated heparin is also safe for patients with renal disease. Unfractionated heparin is associated with HIT and osteoporosis with long-term use and requires regular blood tests for monitoring effects. Unfractionated heparin remains the most common parenteral agent in the treatment of patients with acute coronary syndromes (ACSs). Each of the LMWHs differs significantly in physiological effects, biochemical signature, and pharmacological profile because they were developed individually for a specific indication. In general, LMWHs inhibit factor Xa and antithrombin activity. However, agents within this class are not interchangeable, nor are they a substitute for UFH. Each agent is considered unique by the Food and Drug Administration and World Health Organization. Although LMWHs have gradually replaced heparin for the prevention of deep vein thrombosis, the evidence for these agents for interventional and surgical procedures is still being established. Although LMWHs have demonstrated a somewhat greater effectiveness for ACS, like UFH, these agents also confer a
risk of major bleeding. Low-molecular-weight heparins offer advantages compared with UFH related to ease of dosing, and daily blood test monitoring is not required. The risk for HIT is reduced but not eliminated when using LMWHs.

Whereas traditional agents such as UFH and LMWHs are polytherapeutic, newer agents such as pentasaccharides are monotherapeutic in that these agents do not provide additional therapeutic effects like the heparins such as modulating thrombin-mediated activation of tissue factor pathway inhibitor at vascular sites, antithrombin, and profibrinolytic actions. The physiological basis of fondaparinux lies where the intrinsic and extrinsic coagulation pathways merge and factor X. Theoretically, control of factor X activity reduces but does not inhibit thrombin generation, which may reduce the risk of bleeding during treatment because blood coagulation is still possible. Fondaparinux (Arixtra; Sanofi-Synthelabo/Organon, Bridgewater, NJ) became the first drug licensed for clinical use from the pentasaccharide factor X inhibitor class of anticoagulants.

Fondaparinux is heparinomimetic in that the drug binds to antithrombin III, which then facilitates the binding of antithrombin III to factor Xa, interrupting the blood coagulation cascade. Binding changes the antithrombin molecule enhancing the inhibitory effects. Fondaparinux has no significant effect on factor IIa (thrombin) or platelet aggregation, which makes this agent distinct from UFH and LMWHs. Activated factor VII can partially reverse the anticoagulant effects. Platelets exposed to fondaparinux do form antihemiplatelet antibodies. However, because fondaparinux does not bind to platelets and binds only to antithrombin, HIT and osteoporosis are not a risk.

This synthetic anticoagulant has desirable pharmacokinetics, which includes superior bioavailability, predictable dose effects, no animal or viral contaminants, and no interaction with platelet factor 4 or heparin antibody. Administration by SC route results in rapid onset with no evidence of metabolism. The lack of nonspecific protein binding or drug interactions and a fixed dose across a range of patient weights make this new weapon against clot attractive. Activated clotting time monitoring is not needed for once-a-day dosing, and fondaparinux does not affect the activated partial thromboplastin time or prothrombin time. There is no antidote, and drug levels can be determined only by anti-Xa assays.

Half-life ranges from 14 to 20 hours in healthy volunteers, and peak plasma levels are achieved 2 hours after dosing. Steady state is achieved in 3 to 4 days of repeated once-daily dosing. Distribution seems to be limited to the vascular space, and elimination takes place through renal pathways. Clearance is reduced in renal disease and in patients weighing less than 50 kg.

Fondaparinux is contraindicated in patients with creatinine clearance less than 30 mL/min and should not be administered to patients actively bleeding. In Europe, fondaparinux is indicated for thrombus prevention in patients with ACS, including patients with ST-segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), and unstable angina.

**SIGNIFICANT RESEARCH**

In the OASIS-5 trial of 20,078 patients, 2.5 mg/d fondaparinux for less than 8 days was noninferior to enoxaparin 1 mg/kg twice daily in patients with normal renal function in reducing death or ischemia at 9 days. This efficacy was maintained for up to 6 months for patients with unstable angina or NSTEMI. Major bleeding events, death, and reinfarction at 30 days were significantly lower for patients with STEMI who received fondaparinux compared with those who received standard care including UFH.

In the OASIS-6 trial, in patients with ACS presenting as STEMI who received 2.5 mg fondaparinux via SC route for less than 8 days following an intravenous dose on day 1, death and reinfarction were significantly less compared with patients who received standard care. For patients requiring percutaneous coronary intervention, fondaparinux provided outcomes similar to enoxaparin for NSTEMI or UFH in patients with STEMI.

Additional evidence suggests that fondaparinux may be more effective than enoxaparin in preventing VTE in patients after orthopedic surgery and as effective as UFH with enoxaparin in patients with pulmonary embolism or deep vein thrombosis. Reported side effects include nausea, vomiting, dizziness, and rash, and similar to enoxaparin, 5% of patients may develop significant thrombocytopenia. Bleeding risk may be higher with fondaparinux; however, further research is needed to determine if the risk is significantly different from LMWHs. Current evidence suggests that there are no significant differences for fatal bleeding, critical organ bleeding, operations, infection, and increased length of stay or hospital readmission with fondaparinux.

**CURRENT PRACTICE**

Despite the effective chemical arsenal available for clinicians, VTE prophylaxis is underused. Patients and clinicians need an oral anticoagulant to replace warfarin that targets factors Xa and IIa. However, bringing an oral agent to market will be an expensive undertaking because of the large sample size and extended follow-up required.

For now, keep watch over fluid evidence-based practice guidelines to guide prescribing and monitoring interventions. For guidance regarding all available parenteral anticoagulants, the eighth edition of the American College of Chest Physicians Clinical Practice Guidelines is very helpful for prescribing and practice decisions.

With regard to fondaparinux use during pregnancy, reports are very limited and anecdotal. Further research is necessary for this population. Current recommendations are limited to heparins that do not cross the placenta. Low-molecular-weight heparins are preferred over UFH related to a longer half-life and presumed fewer side effects. However, UFH is preferred during the period close to delivery related to dosing and opportunity for reversal. For women with high risk of HIT or allergy requiring anticoagulation, fondaparinux is an option.

**References**

