An updated statement by the American Heart Association (AHA) on the pharmacology and clinical use of heparin and low-molecular-weight heparin (LMWH) is published online at http://www.atvb.org and also appears in the June 19, 2001 issue of Circulation. The following is a summary of the AHA statement. We have not cited references; these can be accessed from the full text.

Mechanism of Action and Pharmacology of Unfractionated Heparin

Heparin is a sulfated polysaccharide with a molecular weight range of 3000 to 30 000 Da (mean, 15 000 Da). It produces its major anticoagulant effect by inactivating thrombin and activated factor X (factor Xa) through an antithrombin (AT)-dependent mechanism. Heparin binds to AT through a high-affinity pentasaccharide, which is present on about a third of heparin molecules. For inhibition of thrombin, heparin must bind to both the coagulation enzyme and AT, whereas binding to the enzyme is not required for inhibition of factor Xa. Molecules of heparin with fewer than 18 saccharides lack the chain length to bridge between thrombin and AT and therefore are unable to inhibit thrombin. In contrast, very small heparin fragments containing the pentasaccharide sequence inhibit factor Xa via AT. By inactivating thrombin, heparin not only prevents fibrin formation but also inhibits thrombin-induced activation of platelets and of factors V and VIII.

See page e9

The main limitation of heparin results from its propensity to bind to positively charged proteins and surfaces. Pharmacokinetic limitations are caused by AT-independent binding of heparin to plasma proteins, proteins released from platelets, and endothelial cells, resulting in a variable anticoagulant response and the phenomenon of heparin resistance. AT-independent binding to macrophages and endothelial cells also results in dose-dependent clearance. Other limitations include (1) the inability of heparin to inactivate factor Xa in the prothrombinase complex or thrombin bound to fibrin or to subendothelial surfaces and (2) the complications of heparin-induced thrombocytopenia and osteopenia.

Because the anticoagulant response to heparin varies among patients with thromboembolic disorders, it is standard practice to adjust the dose of heparin and monitor its effect by measurement of the activated thromboplastin time (APTT) or, when very high doses are used, by the activated clotting time (ACT).

The value of the APTT is limited because commercial APTT reagents vary considerably in responsiveness to heparin. The APTT should be measured ∼6 hours after a bolus dose of heparin, and the continuous intravenous (IV) dose should be adjusted according to the result. Various heparin-dose-adjustment nomograms have been developed, but none are applicable to all APTT reagents, and the therapeutic range must be tailored accordingly. Standardization can be achieved by calibration against plasma heparin concentration by using a therapeutic range of 0.3 to 0.7 U/mL, based on an anti–factor Xa chromogenic assay, or a heparin level of 0.2 to 0.4 U/mL, by protamine sulfate titration. The dose of heparin should be reduced when used concurrently with fibrinolytic agents or IV platelet glycoprotein (GP) IIb/IIIa receptor antagonists.

Clinical Use of Heparin

Heparin is effective for prevention and treatment of venous thrombosis and pulmonary embolism (PE), for prevention of mural thrombosis after myocardial infarction (MI), and for treatment of patients with unstable angina and MI. Although heparin is used to prevent acute thrombosis after coronary thrombolysis, recent reports question the benefits of heparin in this setting when patients are also treated with aspirin.

Treatment of Venous Thromboembolism

Patients with acute venous thromboembolism (VTE) should receive initial treatment with heparin or LMWH. A loading dose of 5000 U heparin should be given, followed by a continuous infusion of at least 30 000 U every 24 hours and adjusted by a validated nomogram to maintain a therapeutic effect. The targeted APTT range should correspond to a therapeutic range of 1.5 to 2.5 units, based on a heparin level of 0.2 to 0.4 U/mL, by protamine sulfate titration. The dose of heparin should be reduced when used concurrently with fibrinolytic agents or IV platelet glycoprotein (GP) IIb/IIIa receptor antagonists.

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Prophylaxis of VTE
Heparin in a fixed, low dose of 5000 U subcutaneously (SC) every 8 or 12 hours reduces the risk of venous thrombosis and fatal PE by 60% to 70% and is an effective and safe form of prophylaxis in medical and surgical patients at risk of VTE. Although low-dose heparin is also effective in reducing deep-vein thrombosis after hip surgery, it is not as effective as LMWH in this setting.

Coronary Artery Disease
The totality of evidence supports the view that IV heparin reduces death and MI in patients with acute coronary syndromes. Specifically, IV heparin is effective when combined with aspirin in unstable angina. It is probably also effective as an adjunct to aspirin and certain thrombolytic agents in patients with evolving MI, and when combined with IV platelet GP IIb/IIIa antagonists in those undergoing high-risk coronary angioplasty. When used with thrombolytic agents or GP IIb/IIIa antagonists, IV heparin in full doses increases the risk of bleeding, and therefore, the dose should be reduced.

When used in combination with aspirin in patients with unstable angina or non–Q-wave MI, heparin reduces the short-term rates of cardiovascular death and MI by ≈30% compared with aspirin alone. In patients with large anterior infarctions, moderate-dose heparin (12 500 U SC every 12 hours) reduces the incidence of mural thrombosis detected by 2-dimensional echocardiography by >50%.

The effectiveness of heparin as an adjunct to fibrinolytic therapy and aspirin in acute MI is uncertain. The results of angiographic studies assessing coronary patency have yielded conflicting findings, whereas in large clinical trials, heparin has shown a small benefit at the cost of increased bleeding. In a pooled analysis of 6 small, randomized trials evaluating tissue plasminogen activator, there was a trend toward reduced in-hospital mortality with heparin but a significantly higher rate of hemorrhagic complications when heparin was used in tissue plasminogen activator–treated patients.

Recommendations for heparin in patients with acute MI are provided in the American College of Cardiology/AHA guidelines. The intensity of the suggested heparin regimen is influenced by whether thrombolytic therapy is given, the type of thrombolytic agent used, and the presence or absence of risk factors for systemic embolism.

Coronary Angioplasty
In patients undergoing percutaneous transluminal coronary angioplasty, it is standard practice to give heparin, commencing with either an IV bolus of 10 000 U followed by repeated smaller bolus injections as required or a weight-adjusted dose regimen of 100 to 175 U/kg followed by 10 to 15 U/kg per hour. The dose is adjusted to maintain the ACT at >300 to 350 seconds because there is some evidence that the complication rate is higher with lower ACT values. When these high-dose regimens are used in combination with abciximab in addition to aspirin, however, heparin increases the risk of major bleeding. The risk can be reduced without compromising efficacy by lowering the bolus dose of heparin to 70 U/kg, giving additional doses as needed to achieve an ACT >200 seconds, and removing arterial sheaths only after the ACT falls below 150 to 180 seconds. Postprocedural heparin infusions are not needed for most patients who are treated with a combination of aspirin and ticlopidine or aspirin and clopidogrel after coronary angioplasty.

Atrial Fibrillation
Heparin is sometimes given as an alternative to oral anticoagulation perioperatively in high-risk patients with chronic atrial fibrillation who are undergoing elective surgery. Heparin may also be indicated in selected patients for the acute treatment of embolic stroke and before early pharmacological or electrical cardioversion in patients free of atrial thrombus from transesophageal echocardiography.

Low-Molecular-Weight Heparins
LMWHs are derived from heparin by chemical or enzymatic depolymerization to yield fragments approximately one third the size of heparin. LMWHs have a mean molecular weight of 4500 to 5000 Da with a distribution of 1000 to 10 000 Da. All of the anticoagulant, pharmacokinetic, and other biological differences between unfractionated heparin (UFH) and LMWH can be explained by the relatively lower binding properties of LMWH. Compared with UFH, LMWHs have reduced ability to inactivate thrombin because the smaller fragments cannot bind simultaneously to AT and thrombin. In contrast, because bridging between AT and factor Xa is less critical for anti–factor Xa activity, the smaller fragments inactivate factor Xa almost as well as do larger molecules. Because virtually all heparin molecules contain at least 18 saccharide units, UFH has an anti–factor Xa to anti–factor IIa ratio of 1:1. In contrast, commercial LMWHs have an anti–factor Xa to anti–factor IIa ratios between 2:1 and 4:1, depending on their molecular size distribution.

Reduced binding to plasma proteins and cells is responsible for the more predictable dose-response relationship of LMWH, longer plasma half-life (compared with UFH), and lower risk of heparin-induced thrombocytopenia and osteopenia. LMWHs are cleared principally by the renal route.

Prevention of Venous Thrombosis
In general surgical patients and in medical patients at high risk of venous thrombosis, low doses of LMWH administered SC once daily are at least as effective and safe as low-dose UFH administered SC 2 or 3 times daily. LMWH has become the anticoagulant of choice for the prevention of venous thrombosis during major orthopedic surgery and in anticoagulant-eligible victims of major trauma. The risk of bleeding with LMWH is small and comparable to that with low-dose UFH.

Treatment of VTE
LMWHs are administered in weight-adjusted doses by SC injection and are not monitored. Depending on the LMWH agent, a dose of 100 anti–factor Xa units per kilogram twice daily or of 150 to 200 anti–factor Xa units per kilogram daily is given. Although laboratory monitoring is not usually required, the anti–factor Xa level should be checked in patients with renal insufficiency, morbid obesity, and pregnancy because the pharmacokinetic properties, efficacy, and safety of LMWHs are not well established in these situations. LMWH preparations are at least as effective and safe as IV heparin for the treatment of deep-vein thrombosis and PE, and the rates of recurrent thromboembolism and major
bleeding are similar with all of the LMWH preparations that have been evaluated. Out-of-hospital administration of LMWH to eligible patients with deep vein thrombosis is as effective and safe as IV heparin administered in hospital. Once-daily administration of 2 different LMWH preparations is as effective and safe as twice-daily dosing.

Acute Coronary Syndromes
LMWHs administered SC without laboratory monitoring is more effective than placebo in patients with unstable angina and non-Q-wave MI, but no further benefit is observed when a moderate dose is continued over the long term. Studies with the LMWHs dalteparin and nadoparin have demonstrated that they are as effective and safe as heparin. In contrast, 2 studies with enoxaparin reported that this LMWH is more effective than UFH. Potential explanations include true therapeutic differences between the LMWH agents, differences in trial design, the way in which UFH was administered, differences in patient populations, or the play of chance. To determine definitively whether enoxaparin is superior to other LMWH preparations would require multiple direct comparisons in an appropriately powered study.

Experience with LMWH in patients with acute Q-wave MI or in patients with prosthetic heart valves is too limited to allow recommendations to be made.
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