Heparin: Mechanism of Action, Pharmacokinetics, Dosing Considerations, Monitoring, Efficacy, and Safety

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Heparin is the anticoagulant of choice when a rapid anticoagulant effect is required because its onset of action is immediate when administered by intravenous injection. Heparin is administered in low doses when used for primary prophylaxis and high doses when used therapeutically to prevent recurrent thrombosis. Its use is almost always limited to an in-hospital setting because it must be administered parenterally. When heparin is given in therapeutic doses, its anticoagulant effect must be monitored and the dosage must be adjusted frequently. When long-term anticoagulant therapy is indicated, in-hospital heparin administration is usually followed by treatment with oral anticoagulants. A period of overlap of approximately four days should be used, during which time both anticoagulants are given in combination. Long-term out-of-hospital heparin treatment is used when anticoagulant therapy is indicated in pregnancy and in the rare patient who has development of recurrent venous thromboembolism while being treated with appropriate doses of oral anticoagulants.

Heparin is effective and indicated for the prevention of venous thromboembolism (level I) (see "Prevention of Venous Thromboembolism" by Clagett et al in this issue), for the treatment of venous thromboembolism (level I) for the early treatment of patients with unstable angina (level I) and acute myocardial infarction (level I) in patients who have cardiac surgery under cardiac bypass (level I) (new chapter), who have vascular surgery (level III), and in selected patients with disseminated intravascular thrombosis (level III).

In this chapter, the mechanism of action of heparin, its pharmacokinetics, anticoagulant effects, and laboratory monitoring will be reviewed. The clinical use of heparin will be summarized briefly since this is discussed in detail in other chapters. In addition, the potential of a new class of heparins, the low molecular weight heparins (LMWHs) will be discussed and their biophysical, pharmacokinetics, antithrombotic, and hemorrhagic properties will be compared with standard heparin.

Structure and Mechanism of Action of Heparin

Heparin is a glycosaminoglycan (GAG) composed of chains of alternating residues of D-glucosamine and a uronic acid.1 Its major anticoagulant effect is accounted for by a unique pentasaccharide with a high affinity binding sequence to antithrombin III (ATIII).2–4 The unique sequence is present in only one third of heparin molecules.1,4,5 The anticoagulant effect of heparin is mediated largely through its interaction with ATIII;1,4–7 this produces a conformational change in ATIII and so markedly accelerates its ability to inactivate the coagulation enzymes thrombin (factor IIa), factor Xa, and factor IXa.3 Of these three enzymes, thrombin is the most sensitive to inhibition by heparin/ATIII.3,4,5–7

Heparin catalyzes the inactivation of thrombin by ATIII by acting as a template to which both the enzyme and inhibitor bind to form a ternary complex.3,4,5,6,7,9–11 In contrast, the inactivation of factor Xa by ATIII/heparin complex is achieved by binding of the enzyme to ATIII only and does not require ternary complex formation.1,4,5,6,7,9,11 Heparin molecules that contain fewer than 18 saccharides are unable to bind thrombin and ATIII simultaneously and, therefore, are unable to accelerate the inactivation of thrombin by ATIII, but retain their ability to catalyze the inhibition of factor Xa by ATIII.1,4,5,6,7,9–11 (Fig 1). Heparin also catalyzes the inactivation of thrombin by a second plasma cofactor, heparin cofactor II (HCII).11 This second anticoagulant effect of heparin is specific for thrombin, it does not require the unique ATIII-binding pentasaccharide, and it is achieved only at very high doses of heparin.12–15

Heparin is heterogeneous with respect to molecular size, anticoagulant activity, and pharmacokinetic properties. The molecular weight of heparin ranges from 5,000 to 30,000 with a mean molecular weight of 15,000 (approximately 50 monosaccharide chains).16–18 The anticoagulant activity of heparin is heterogeneous because of the following: (1) only one third of the heparin molecules administered to patients have anti-
coagulant activity; (2) the anticoagulant profile of heparin is influenced by the chain length of the molecules; and (3) the clearance of heparin is influenced by its molecular size, with the higher molecular weight species being cleared from the circulation more rapidly than the lower molecular weight species. This differential clearance phenomenon results in an accumulation in vivo of the lower molecular weight species that have a reduced ratio of antithrombin to anti-factor Xa activity. This effect is responsible for the differences observed when the relationship between the heparin level and the activated partial thromboplastin time (APTT) is assessed in vivo and in vitro, since the lower molecular weight species that are retained in vivo are measured in the anti-factor Xa heparin assay but have minimal effects on the APTT.

Administration, Pharmacokinetics, and Pharmacodynamics

Heparin is not absorbed after oral administration and, therefore, must be given by injection. The two preferred routes of administration are intravenous and subcutaneous. Intramuscular injection can produce large hematomas caused by accidental puncture of an intramuscular vein and, therefore, should be avoided. There is evidence that heparin administered by intermittent injection is associated with more bleeding than when it is administered by the continuous intravenous route,39 the latter method is, therefore, preferred if heparin is administered intravenously. The efficacy and safety of heparin administered by either the continuous intravenous method or by the subcutaneous route are comparable provided that the dosages used are adequate.39,40 If, however, the subcutaneous route is selected, the initial dose must be sufficiently high to counteract the reduced bioavailability that occurs when heparin is administered by the subcutaneous route.41 If an immediate anticoagulant effect is required and heparin is administered by subcutaneous injection, the initial dose should be accompanied by an intravenous bolus injection because an anticoagulant effect from subcutaneous heparin is delayed for 1 to 2 h.

Following its injection and passage into the bloodstream, heparin binds to a number of plasma proteins, including histidine-rich glycoprotein (HRGP),42-44 platelet factor IV (PFIV),45-47 vitronectin,46 fibrinogen,47 and von Willebrand factor (VWF).48 The binding of heparin to these proteins contributes to its reduced plasma recovery (bioavailability) at low concentrations, to the variability of the anticoagulant response to fixed doses of heparin in patients with thromboembolic disorders,49 and to the laboratory phenomenon of heparin resistance.50 Binding of heparin to VWF results in the inhibition of VWF-dependent platelet function.48

Heparin also binds to endothelial cells and macrophages,50 a property that contributes to its complicated pharmacokinetics. Heparin is cleared through a combination of a rapid saturable and a much slower first-order mechanism of clearance.50-54 The saturable phase of heparin clearance is thought to be due to heparin binding to receptors on endothelial cells55-56 and macrophages57 where it is internalized, depolymerized, and metabolized into smaller and less sulfated forms.58,59 Clearance through the slower nonsaturable mechanism is largely renal. At therapeutic doses a considerable proportion of the administered heparin is cleared through the rapid saturable, dose-dependent mechanism of clearance. Because of these kinetics, the anticoagulant response to heparin at therapeutic doses is not linear but increases disproportionately both in its intensity and duration with increasing dose. Thus, the apparent biologic half-life of heparin increases from approximately 30 min with an intravenous bolus of 25 U/kg, to 60 min with an intravenous bolus of 100 U/kg, to 150 min with a bolus of 400 U/kg.52-54

The plasma recovery of heparin is reduced50 when the drug is administered by subcutaneous injection in low doses (eg, 5,000 U/12 h) or moderate doses of 12,500 U/12 h60 or 15,000 U/12 h.41 However, at high therapeutic doses of heparin (>35,000 U/24 h), the plasma recovery is almost complete.40 The poor bioavailability of heparin when administered by subcutaneous injection occurs because as heparin enters the intravascular space slowly from subcutaneous depots, it binds to saturable sites on endothelial cells and macrophages where it is internalized and metabolized. Circulating plasma levels are achieved only after these cell surface receptors are saturated, either by a large loading dose or by the cumulative effects of a number of moderately high doses. The difference between the bioavailability of heparin when administered by subcutaneous or intravenous injection was demonstrated strikingly in a study of patients with venous thrombosis.61 The patients were randomized to receive either 15,000 U of heparin/12 h by subcutaneous injection.
or 30,000 U of heparin by continuous intravenous infusion; both regimens were preceded by an intravenous bolus dose of 5,000 U. Therapeutic heparin levels and APTT ratios were achieved at 24 h in only 37 percent of patients who were randomized to receive subcutaneous heparin, while therapeutic heparin levels and APTT ratios were achieved at 24 h in 71 percent given an identical dose of heparin by continuous intravenous infusion.

**Laboratory Monitoring and Dose-Response Relationships of Heparin**

The anticoagulant effects of heparin are usually monitored by the APTT, a test that is sensitive to the inhibitory effects of heparin on thrombin, factor Xa, and factor IXa. When heparin is administered in fixed doses, the anticoagulant response to heparin varies among sick patients, including those with acute venous thromboembolism\(^62\) and with myocardial ischemia.\(^61,65-66\) This variability is caused by differences between patients in their plasma concentrations of heparin-neutralizing plasma proteins and in their rates of heparin clearance. There is evidence from subgroup analysis of cohort studies (level III) that a relationship exists between the clinical effectiveness of heparin and its effect \(\text{ex vivo}\) on the APTT for the following conditions: prevention of recurrent thrombosis in patients with proximal vein thrombosis;\(^41,48\) prevention of mural thrombosis in patients with acute myocardial infarction;\(^61\) prevention of recurrent ischemia in patients following streptokinase therapy for acute myocardial infarction\(^63,64\) and in the prevention of coronary artery reocclusion after thrombolytic therapy with tissue plasminogen activator\(^69\) (Table 1). For this reason, the dose of heparin administered to patients should be monitored by laboratory testing and adjusted to achieve a therapeutic level; this anticoagulant effect is referred to as the "therapeutic range."

**Table 1—Relationship Between Failure to Reach Lower Limit of Therapeutic Range and Thromboembolic Events From Subgroup Analysis of Prospective Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Patients</th>
<th>Outcome</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hull et al(^a)</td>
<td>DVT</td>
<td>Recurrent VTE</td>
<td>15.0</td>
</tr>
<tr>
<td>Basu et al(^b)</td>
<td>DVT</td>
<td>Recurrent VTE</td>
<td>10.7</td>
</tr>
<tr>
<td>Turpie et al(^c)</td>
<td>AMI</td>
<td>LVMT</td>
<td>22.2(\pm)</td>
</tr>
<tr>
<td>Kaplan et al(^d)</td>
<td>AMI</td>
<td>Recurrent M/AP</td>
<td>6.0(\pm)</td>
</tr>
<tr>
<td>Camilleri et al(^e)</td>
<td>AMI</td>
<td>Recurrent M/AP</td>
<td>13.3</td>
</tr>
<tr>
<td>De Bono et al(^b)</td>
<td>AMI</td>
<td>Coronary Artery Patency</td>
<td>8.5</td>
</tr>
</tbody>
</table>

\(\text{DVT} = \text{deep vein thrombosis}; \text{AMI} = \text{acute myocardial infarction}; \text{VTE} = \text{venous thromboembolism}; \text{LVMT} = \text{left ventricular mural thrombosis}; \text{AP} = \text{angina pectoris}.)

\(^a\)Estimated by assuming a normal distribution of the reported heparin levels.

\(^b\)Kaplan used a PTT measurement and reported the relative risk associated with PTT values less than 50 s compared with PTT values of more than 100 s.

The recommended therapeutic range for the APTT for the treatment of venous thrombosis is based on a study performed in rabbits\(^67\) that demonstrated that thrombus extension was prevented by a heparin dose that prolonged the APTT ratio to 1.5 to 2.5, corresponding to a heparin level by protamine titration of thrombin time of 0.2 to 0.4 U/ml.

Unfortunately, the different commercial APTT reagents vary in their responsiveness to heparin.\(^68,69\) For many APTT reagents, a therapeutic effect is achieved by an APTT ratio of 1.5 to 2.5 (measured by dividing the observed APTT by the mean of the laboratory control APTT). With very sensitive APTT reagents, the therapeutic range is higher than a ratio of 1.5 to 2.5, while for insensitive reagents the therapeutic range is lower. The difference in responsiveness of various APTT test systems to the anticoagulant effects of heparin has been assessed by the College of American Pathologists and the UK External Quality Assessment surveys and is shown in Figure 2. Technical variables that affect the APTT response to heparin are the type of clot detection system, the contact activator, and the phospholipid composition of the reagent.\(^69\) Important variations in the responsiveness to heparin between different batches of the same brand of APTT reagent have also been reported.\(^70\) The response of the APTT ratio to heparin is reduced by the elevated levels of procoagulants that occur in a number of clinical states, including pregnancy, malignancy, acute thrombosis, and major surgery. Some APTT systems are accelerated by the procoagulants more than others giving different APTT ratios with the same concentrations of heparin. An ideal APTT system should give a linear relationship over a clinically relevant anticoagulant range. Efforts are being made to develop standards for the APTT system, but an international standard is not yet available. Until there is a reliable system of APTT standardization for heparin monitoring, therapeutic ranges should be established in each local laboratory. An approximation of the therapeutic range of 0.2 to 0.4 U/ml of heparin (by protamine titration) can be made by testing the APTT reagent in a plasma system that has been calibrated by addition of a range of clinically relevant concentrations of heparin. A cumbersome but more accurate method is to compare APTT ratios with measured heparin levels (by protamine titration) in plasma samples obtained from patients treated with heparin.

Although there is good evidence that APTT ratios above the lower limit of the therapeutic range are associated with protection against thrombosis,\(^41,45,53-66\) maintaining the APTT in the therapeutic range does not guarantee protection from bleeding complications. The risk of bleeding complications is increased with increasing heparin dose\(^71,72\) (which in turn is related to the anticoagulant response), but other clinical
Factors, particularly recent surgery, trauma, invasive procedures, an occult local lesion (such as an ulcer, renal calculus, or malignant neoplasm), or a generalized hemostatic abnormality are at least as important predictors of bleeding during heparin treatment.

A less intense anticoagulant effect is required to prevent venous thrombosis with heparin than to treat established thrombosis. Low-dose heparin, 5,000 U subcutaneously two or three times daily, is highly effective in preventing venous thrombosis in moderate-risk patients and is administered without laboratory monitoring. However, in very high-risk patients such as those having hip surgery, the incidence of thrombosis is approximately 25 percent and of proximal vein thrombosis it is 10 to 15 percent, despite low-dose heparin prophylaxis. The results of three studies have demonstrated that the efficacy of low-dose heparin therapy is improved without compromising safety by adjusting the dose to achieve a minimal heparin effect, in all three, adjusted low-dose heparin therapy was significantly more effective than fixed-dose heparin therapy following hip surgery. In two of the studies, the APTT was prolonged slightly (APTT ratio 1.1 to 1.2), which required a mean daily dose of heparin in excess of 18,000 U, while in the other study the APTT was maintained in the upper normal range and the mean daily dose of heparin was approximately 15,000 U. The adjusted dose regimen has limitations for routine use since it requires careful monitoring and the use of a responsive APTT system. Nevertheless, these three studies illustrate the important principle that a small heparin effect by ex vivo measurement is required for optimal prophylaxis in very high-risk patients.

Details of heparin treatment for the different indications are provided in separate chapters. A rapid therapeutic heparin effect is achieved by commencing with a loading dose of 5,000 U as an intravenous bolus followed by 32,000 U/24 h by continuous infusion. A lower dose of 24,000 U/24 h might provide adequate protection immediately after thrombolytic therapy. The APTT should be performed at approximately 6 h after the bolus and the heparin dose adjusted according to the result obtained. A heparin dose adjustment nomogram has been developed for a specific APTT reagent for which the therapeutic range is 1.9 to 2.7 times control (based on a heparin level of 0.2 to 0.4 U/ml). This nomogram is not applicable to all APTT systems but can be adapted to other systems by the local laboratory. In patients with acute myocardial infarction who receive thrombolytic therapy, the lytic state often induces a transient coagulation defect that can prolong the APTT for up to 24 h. Therefore, the dose of heparin should only be adjusted upwards in the first 24 h if the APTT is below the therapeutic range. A modified nomogram in which a high initial dose is used has also been shown to be effective in patients at low clinical risk for bleeding.

It is also possible to achieve therapeutic heparin levels with subcutaneous injection, but the anticoagulant effect of subcutaneous heparin is delayed for approximately 1 h and peak levels occur at approximately 3 h. If the subcutaneous route is selected, a high initial dose should be used (35,000 U/24 h in two divided doses) to overcome the poor bioavailability of moderate doses. If a rapid effect is required, the subcutaneous injection should be preceded by an intravenous bolus of 5,000 U. Monitoring is performed 6 h after injection with the aim of maintaining the APTT in the therapeutic range at this time.

**SIDE EFFECTS**

**Bleeding**

Bleeding is a major complication of heparin. Heparin can also produce other less common but serious complications. These are listed in Table 2. Of these,
Thrombocytopenia and thrombosis

Thrombocytopenia was for established venous thromboembolism and their osteoporosis while none of the control patients had this complication. In all patients, serum calcium, phosphorus, and alkaline phosphatase values were within normal limits.

Except for one report, the daily dose of heparin was 15,000 U or more. In three studies, the duration of treatment was five months or less, while in all other reports treatment was in excess of six months.

In the descriptive study (level IV) by Griffith and associates, which initially drew attention to a possible association, six of ten patients who received between 15,000 and 20,000 U daily for greater than six months had development of clinical osteoporosis. None of 107 patients receiving lower doses had this complication develop.

In the other randomized controlled trial, Howell and associates reported that 1 of 20 women allocated to receive long-term antenatal heparin prophylaxis (10,000 U twice daily) had development of clinical osteoporosis while none of the control patients had this complication develop. This study is classified as level II because the number of patients in this trial was too small to provide a reasonable chance of demonstrating a clinically important difference. Thus, the 95 percent confidence intervals on the observed incidence of 5 percent varies from 0.13 percent to 24.87 percent.

Recently, Dahlman and associates reported on 70 women who received heparin therapy during pregnancy and 30 control subjects who had roentgenograms of the spine and hips one week post partum (level III). Twenty-five of the women received heparin for established venous thromboembolism and their average daily heparin dose was 31,400 U. The remaining 45 women received prophylactic heparin because of a history of thromboembolism; 24 received a high-dose regimen, average dose 17,500 U daily. Of the patients who received heparin, 12 (17 percent) had obvious osteopenia on roentgenogram compared with none in the control group. Two women who received the high-dose prophylactic regimen had development of symptomatic spinal fractures postpartum. There was a relationship between the duration of heparin therapy and osteopenia.

Ginsberg and associates have recently reported the results of a case-control study (level III) that provides further evidence for an association between heparin and osteoporosis. Sixty-one women who had received heparin for greater than one month were matched with 61 control subjects for age, parity, and duration since last pregnancy. All patients underwent dual photon absorptiometry of the lumbar spine and single photon absorptiometry of the wrist to assess bone density. There was a statistically significantly greater proportion of cases than controls with abnormally low bone density. Although none of the cases suffered symptomatic fractures, the lower bone density in these patients suggests that long-term heparin therapy has the potential to produce clinical osteoporosis in a small percentage of exposed subjects.

The mechanism for heparin-associated osteoporosis is not clear. Ambrus and associates demonstrated that the administration of heparin for three months to female mice can lead to significant loss of body calcium. Avioli reviewed the possible pathophysiologic features of heparin-associated osteoporosis and the following mechanisms were suggested: (1) potentiation of parathyroid hormone (PTH) effect on osteoclast activity; (2) decreased osteoblast activity; (3) increased bone resorption due to heparin-related collagenase activity; and (4) abnormalities in vitamin D metabolism.

It has been suggested that heparin's affinity for calcium leads to decrease in ionized calcium, which results in PTH overactivity and subsequent demineralization of bone. However, the absence of clinical evidence of parathyroid hyperplasia in patients with heparin-associated osteoporosis and the fact that the administration of heparin to PTH-deficient animals can lead to bone resorption and decreased bone formation make the role of PTH in the pathogenesis of heparin-associated osteoporosis unlikely.

In summary, although level I studies assessing the relationship between heparin exposure and osteoporosis have not been performed, it is likely that long-term heparin therapy produces osteoporosis in a small percentage of exposed individuals. The limited evidence suggests that there is a dose effect. Short-term heparin therapy (14 days or less) is unlikely to be associated with clinically important osteoporosis. It is

**Table 2—Side Effects of Heparin**

<table>
<thead>
<tr>
<th>Side Effects of Heparin</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Bleeding</td>
<td>Common</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Thrombocytopenia and thrombosis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Anaphylactic reactions</td>
<td>Rare</td>
</tr>
<tr>
<td>Skin necrosis</td>
<td>Rare</td>
</tr>
<tr>
<td>Local urticaria</td>
<td>Rare</td>
</tr>
<tr>
<td>Hypocalcosteronism</td>
<td>Rare</td>
</tr>
</tbody>
</table>

the most important are osteoporosis and thrombocytopenia.

**Osteoporosis**

An association between heparin therapy and osteoporosis has been suspected for many years. With the exception of one randomized trial with only 40 patients (level II), the reports have been descriptive series or case reports (level IV and V). In these studies, patients with osteoporosis presented with bone pain and/or radiologic findings that included rib fractures, vertebral collapse, and asymptomatic osteopenia of thoracolumbar vertebrae. In all patients, serum calcium, phosphorus, and alkaline phosphatase values were within normal limits.

In the other randomized controlled trial, Howell and associates have recently reported that the daily dose of heparin to PTH-deficient animals can lead to bone resorption and decreased bone formation make the role of PTH in the pathogenesis of heparin-associated osteoporosis unlikely.

In summary, although level I studies assessing the relationship between heparin exposure and osteoporosis have not been performed, it is likely that long-term heparin therapy produces osteoporosis in a small percentage of exposed individuals. The limited evidence suggests that there is a dose effect. Short-term heparin therapy (14 days or less) is unlikely to be associated with clinically important osteoporosis. It is
also unlikely that three months of treatment with moderate doses of heparin (approximately 20,000 U/24 h) is associated with clinically important osteoporosis.\textsuperscript{101} The vast majority of reports of heparin-associated osteoporosis have been in patients who were treated with at least 20,000 U/d for more than six months. The true incidence of osteoporosis in patients receiving long-term heparin therapy is unknown, but it is likely to be substantial. Therefore, all patients who receive high doses of heparin for more than five months should be considered to have a significant risk of osteoporosis developing.

**THROMBOCYTOPENIA**

Thrombocytopenia is a well-recognized complication of heparin therapy. In most cases, it is asymptomatic but rarely it is associated with arterial thrombosis and even less commonly with bleeding.\textsuperscript{102,103} Most cases of heparin-associated thrombocytopenia have been reported in patients receiving high doses of heparin. Thrombocytopenia has also been reported rarely (less than 1 percent) in patients receiving low-dose heparin prophylaxis\textsuperscript{104,105} and even in patients receiving heparin flushes to maintain patency of intravascular catheters.\textsuperscript{106-109} Thrombocytopenia is more common with heparin derived from bovine lung than from porcine gut.\textsuperscript{102,103} Pooled analysis of studies in which patients were randomized to receive high doses of heparin derived from one or other source of heparin revealed on overall incidence of thrombocytopenia of 15.6 percent in the 173 patients receiving bovine heparin and 5.8 percent in the 223 patients receiving porcine heparin\textsuperscript{102} (level I). Thrombocytopenia usually begins between 3 and 15 days after commencing heparin therapy (median, 10 days),\textsuperscript{102,103} but it has been reported within hours of commencing heparin therapy in patients who have been exposed to heparin previously.\textsuperscript{102,111,112} The platelet count usually returns to baseline levels within four days of stopping heparin therapy.\textsuperscript{107} There are reports of persistent thrombocytopenia for 7 to 14 days\textsuperscript{113-115} and of an elevation of platelet count despite continuation of heparin therapy,\textsuperscript{116-118} but it is uncertain whether the cause of thrombocytopenia in these atypical cases is heparin related.

Heparin-associated thrombocytopenia is thought to be caused by an IgG-heparin immune complex involving both the Fab and Fc portion of the IgG molecule.\textsuperscript{119} In vitro studies of heparin-induced platelet aggregation or release have shown that a number of LMWHs cross-react with heparin when tests are performed on convalescent plasma samples of patients with heparin-associated thrombocytopenia and that the Organon heparinoid, Lomoparin, does not cross-react.\textsuperscript{120} Whether these in vitro findings can be translated into the safe use of Lomoparin in patients with current or past heparin-associated thrombocytopenia is uncertain at present.

Heparin-associated thrombocytopenia can be complicated by thrombotic manifestations caused by platelet-rich thrombi.\textsuperscript{121-126} The incidence of heparin-induced arterial thrombosis has been estimated to be 0.4 percent (4 of 1,080) in patients receiving therapeutic doses of porcine gut heparin (level II). The most common manifestations of thrombosis are lower limb arterial thrombosis, thrombotic cerebrovascular accidents, and myocardial infarction. Venous thrombosis has also been described but it is uncertain whether this is a manifestation of heparin-associated thrombocytopenia or results from heparin resistance that has been described to occur with heparin-associated thrombocytopenia.\textsuperscript{127-129} In most cases of thrombosis, the lowest platelet count ranges from 40,000 to 60,000\textsuperscript{108,109,130-137} but the degree of thrombocytopenia can be very severe with platelet counts as low as 5,000/ ml. Bleeding complications have been described in patients with heparin-associated thrombocytopenia\textsuperscript{132} but they are less frequent and much less important than thrombotic complications. Rarely, heparin-induced thrombosis can be heralded by a fall in platelet count without overt thrombocytopenia, eg, a fall in platelet count from 350,000 to 150,000. For this reason, patients who receive heparin should have a platelet count performed daily and if the platelet count falls more than five percent below the baseline, heparin therapy should be stopped and an alternative management strategy instituted. If warfarin treatment has already been started and the international normalized ratio (INR) is approaching or in the therapeutic range, warfarin therapy can be continued without the addition of alternative treatment. If warfarin therapy has not been started, and heparin is being used to treat venous thromboembolism, a caval filter can be inserted or alternative antithrombotic agents can be

### Table 3—Dosage Regimen for Ancrod

<table>
<thead>
<tr>
<th>Initial dose: 2 U/kg IV over 6 h</th>
<th>Maintenance—either by subcutaneous injection or IV infusion.</th>
<th>A) Subcutaneous injection: subsequent dose based on the fibrinogen level 12 h after IV infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen Level, g/L</td>
<td>Daily subsequent dose of ancrod, U/kg</td>
<td></td>
</tr>
<tr>
<td>&gt;0.5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>0.5 to 1.0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt;1.0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B) Continuous intravenous infusion: subsequent doses by IV infusion based on a fibrinogen level.</td>
<td>Daily IV dose of ancrod, U/kg</td>
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</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>1 over 24 h</td>
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</tr>
<tr>
<td>&gt;0.5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>0.5 to 1</td>
<td>1 over 18 h</td>
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</tr>
<tr>
<td>1.0 to 1.5</td>
<td>1 over 18 h</td>
<td></td>
</tr>
<tr>
<td>1.5 to 2.0</td>
<td>1 over 12 h</td>
<td></td>
</tr>
<tr>
<td>&gt;2.0</td>
<td>1 over 8 h</td>
<td></td>
</tr>
</tbody>
</table>

Heparin (Hirsh et al)
used. Two alternative antithrombotic agents have been evaluated in descriptive studies (level V). These are the snake venom, ancord, and the Organon heparinoid, Lomoparin. A dosage regimen for ancord (which is still experimental in the United States but can be obtained from Knoll Pharmaceutical and stored in the pharmacy for compassionate use) is shown in Table 3.

Patients with a history of heparin-associated thrombocytopenia who require heparin treatment present a difficult problem of management. Although examples of successful reexposure to heparin have been described, this approach is potentially dangerous. There have been a number of case reports of the successful use of LMWHs, but most fractions tested exhibit immunologic cross-reactivity with heparin when tested with convalescent plasma from patients with previous heparin-associated thrombocytopenia. The Organon heparinoid, Lomoparin, which is composed of heparin sulfate, dermatan sulfate, and chondroitin sulfate, exhibits minimal cross-reactivity with heparin and has been used successfully to treat patients with heparin-associated thrombocytopenia. Other LMWHs exhibit cross-reactivity and there are reports of persisting thrombocytopenia during LMWH treatment. Ancrod can also be used for short-term treatment, but its long-term use is limited by the development of antibodies that render patients resistant to its effects.

An immunologic basis for heparin-induced thrombocytopenia and thrombosis has been proposed and confirmed by a number of investigators. More recently, patients with heparin-associated thrombocytopenia have been reported to exhibit heparin IgG immune complexes to platelet Fc receptors with resulting platelet activation. Heparin has been shown to bind to platelets in a specific and saturable fashion, a process that is markedly enhanced after platelet activation. Heparin fractions in the highest molecule weight range and with the more extensive sulfation exhibit the greatest amount of binding.

The diagnosis of suspected heparin-induced thrombocytopenia can be confirmed by laboratory tests, which, however, are rarely useful in making clinical decisions at the time a patient presents. A test based on 14C serotonin release of washed donor platelets plus heat-treated patient serum in the presence of therapeutic (0.1 U/ml and high 100 U/ml) heparin concentrations has been shown to be both sensitive and specific.

OTHER SIDE EFFECTS

Heparin has been reported to produce two distinct types of skin lesions: urticarial lesions and skin necrosis. Urticarial lesions occur at the site of subcutaneous injection and may be caused by a contaminant of heparin. Skin necrosis may or may not be associated with thrombocytopenia. In severe forms of skin necrosis, the tissue requires debridement and skin grafting. The reaction seems to be unrelated to the source of the heparin. The histologic features of heparin-associated skin necrosis are those of a hemorrhagic infarct of the skin and subcutaneous fat with acute necrotizing angitis affecting small dermal vessels and extending into subcutaneous fat, features that are consistent with a hypersensitivity angitis.

White and associates reported eight cases of skin necrosis associated with heparin administration. Six occurred at the site of subcutaneous injection of heparin, but in the other two, skin necrosis occurred in association with the intravenous administration of heparin.

It has been known for some time that heparin inhibits aldosterone synthesis, probably at the step where corticosterone is converted to 18-hydroxycorticosterone. This is usually of no clinical importance, but there are three case reports of heparin-induced hypoaldosteronism leading to hyperkalemia and other metabolic derangements and even death. The hyperkalemia and hypoaldosteronism reverted to normal in two of these cases when heparin therapy was discontinued (and returned on rechallenge in one of these cases). In these cases, the heparin was administered for less than six weeks. In the third case, the patient received therapeutic doses of heparin for four years and died of the consequences of hypoaldosteronism. Thus, selective hypoaldosteronism is a rare but probably real side effect of heparin administration.

Hypersensitivity reactions are well documented but rare. The symptoms include urticaria, conjunctivitis, rhinitis, asthma, cyanosis, tachypnea, oppressive feeling, angioneurotic edema, and anaphylactic shock. In addition, patients receiving heparin occasionally have development of local urticarial-like lesions that rapidly disappear when the drug therapy is discontinued.

Heparin has been associated with priapism in a number of case reports. It is uncertain whether it is the heparin or the underlying thrombotic condition that causes the priapism.

LOW MOLECULAR WEIGHT HEPARINS

The LMWHs are a new class of anticoagulants that have been developed for clinical use. These new compounds are being used in Europe and it is anticipated that they will be approved for use in North America in the next few years.

The clinical development of LMWHs was stimulated by the observation that for equivalent antithrombotic effects in experimental models, LMWHs produced less bleeding than the standard heparin (SH)
from which they were derived.168-173 These observations were followed by clinical studies that demonstrated that LMWHs are effective and safe antithrombotic agents for the prevention and treatment of venous thrombosis.

LMWHs are fragments of heparin, produced by either chemical or enzymatic depolymerization.174 LMWHs are approximately one third of the size of heparin; like standard heparin they are heterogeneous with respect to molecular size, with a molecular weight distribution of 1,000 to 10,000 and a mean molecular weight of 4,000 to 5,000. Depolymerization of heparin results in a change in the anticoagulant profile of the resultant low molecular weight fractions with a progressive loss of their ability to catalyze thrombin inhibition.15,27,175 Two other GAGs have also been developed for clinical use. These are dermatan sulfate and the Organon heparinoid (Lomoparin) which is a mixture of heparan sulfate (the major component making up 80 percent of the mixture) and smaller amounts of dermatan sulfate and chondroitin sulfates.

Anticoagulant Effects of LMWHs

Like heparin, LMWHs produce their major anticoagulant effect by binding to an antithrombin ATIII, through a unique pentasaccharide sequence,5,8,9 which is present on less than one third of LMWH molecules. Since a minimum chain length of 18 saccharides (including the pentasaccharide sequence) is required for ternary complex formation, only the small percentage of the larger LMWH species in each preparation are able to inactivate thrombin. In contrast, all of LMWH fragments that contain the high-affinity pentasaccharide catalyze the inactivation of factor Xa. Virtually all SH molecules contain at least 18 saccharide units while only 25 percent to 50 percent of the different LMWHs contain fragments with 18 or more saccharide units.10,29,30,176,177 Therefore, in contrast to SH that has a ratio of antifactor Xa to antifactor IIa activity of approximately 1:1, the various commercial LMWHs have antifactor Xa to anti-IIa ratios that vary between 4:1 and 2:1 depending on their molecular size distribution.

Pharmacokinetics of LMWHs

The plasma recoveries and pharmacokinetics of heparin and LMWHs differ because of differences in their relative binding properties to plasma proteins and cells. Most heparin-binding proteins do not bind to or neutralize LMWHs.36,42,46-48,178 The absence of protein binding of LMWHs41,42 contributes to their excellent bioavailability at low doses179 and to their predictable anticoagulant response when administered in fixed doses.180 LMWH preparations also have a lower affinity than heparin for VWF,48 a property that could contribute to the observation that LMWHs produce less experimental bleeding than heparin for equivalent anticoagulant effects.168-173,181 Unlike heparin, LMWHs do not bind to endothelial cells in culture,51,182,183 a property that could be responsible for their longer plasma half-life (which is approximately twofold to fourfold longer than heparin).184-190 LMWHs are cleared principally by the renal route and their biologic half-life is increased in patients with renal failure.184,191,192

Antithrombotic and Hemorrhagic Effects of LMWHs, Heparinoids, and Standard Heparin in Experimental Models in Animals

The antithrombotic effects and hemorrhagic effects of heparin have been compared with LMWHs with the Organon heparinoid, Lomoparin, and with dermatan sulfate in a variety of experimental animal models.166-173,178,193-197 In these models of thrombosis, temporary venous stasis is produced by ligating an appropriate vein and blood coagulation is stimulated by injecting either serum, factor Xa, thrombin, or tissue factor.181,196,197 When compared on a gravimetric basis, LMWHs are slightly less effective than heparin as antithrombotic agents, but they produce much less bleeding than heparin in models measuring blood loss from a standardized injury.166-172,193,194,195

These differences in the relative antithrombotic to hemorrhagic effects of these polysaccharides could be due in part to their different effects on platelet function49,196,199 and vascular permeability.200

Clinical Studies

LMWHs have a number of advantages over heparin; they have a longer plasma half-life and a more predictable anticoagulant response to weight-adjusted doses than SH. These properties allow LMWHs to be administered once daily and without laboratory monitoring. The observation in experimental animals that LMWHs produce less bleeding than SH for an equivalent antithrombotic effect allows patients to be treated with higher anticoagulant doses of LMWHs than SH without compromising patient safety. This potential advantage of LMWHs has been demonstrated in one prophylactic study in which SH produces a significant increase in bleeding when its dose was increased to match the anticoagulant effect ex vivo of a LMWH,201 and in two studies comparing high doses of a LMWH with full doses of SH for the treatment of venous thrombosis, LMWHs have been evaluated and compared with heparin in randomized clinical trials for the prevention and treatment of venous thromboembolism.202,203

Prevention of Venous Thrombosis

The results of studies evaluating LMWHs for the prevention of venous thrombosis have been reviewed
For general surgical patients, LMWHs administered once daily by subcutaneous injection have been shown to reduce cardiovascular mortality when compared with placebo and to be approximately 30 percent more effective than SH 5,000 U (administered by subcutaneous injection twice or three times daily) in preventing venous thrombosis without any difference in bleeding.204

When compared with a control group, LMWHs have been shown to reduce the incidence of thrombosis in patients undergoing major knee or hip surgery by about 70 percent without increasing the risk of bleeding.205-207 When compared directly with other forms of prophylaxis in orthopedic patients, LMWHs are significantly more effective than heparin 5,000 U subcutaneously administered twice or three times daily;208,209 significantly more effective than oral anticoagulants;210 significantly more effective than dextran211,212,213 significantly more effective than aspirin (B. Davidson, written communication, 1992); and significantly more effective than adjusted-dose heparin in preventing proximal vein thrombosis.214

LMWHs are very effective in patients with stroke215,216 and in other high-risk medical patients,217 producing a relative risk reduction in venous thrombosis of between 60 percent and 90 percent. This beneficial effect occurred without an increase in clinically important bleeding. LMWHs have also been shown to be significantly more effective than SH in preventing venous thrombosis in patients with paralytic stroke and in patients with spinal cord injury. Thus, in both studies comparing LMWHs with heparin, patients randomized to receive LMWH showed a greater than 70 percent risk reduction in thrombosis, a statistically significant difference.218,219

Treatment of Venous Thrombosis

LMWHs administered in a fixed dose by subcutaneous injection have been compared with dose-adjusted heparin administered by continuous infusion for the treatment of venous thrombosis. The results have been reviewed elsewhere and are discussed in more detail in this supplement. Two different outcome measures have been used. In studies using change in thrombus size assessed by repeating venography at the end of the course of treatment, LMWHs were shown to be as effective or more effective than heparin. In both studies using symptomatic recurrent venous thromboembolism as the outcome measure there was a strong trend for the LMWH to be both more effective and safer than heparin. These findings raise the possibility that selected patients with venous thrombosis might be able to be treated at home, an advance that would reduce cost and improve patient convenience.

More research is required to clarify a number of important issues that have arisen from current studies with LMWHs.

Like heparin,200 LMWHs do not cross the placental barrier,221-223 and descriptive studies suggest they might be safe and effective224 in pregnancy.

When used for the prevention of venous thrombosis, postoperative dosing is effective,201,202,203,204,205,206,207,208,209 but it is unknown whether it is as effective as preoperative administration. The long-term use of heparin can be complicated with osteoporosis. Although there is a case report of successful use of a LMWH in a patient whose treatment with SH was complicated with symptomatic osteoporosis,224 more information from appropriately designed studies will be required before it can be concluded that this rare but troublesome side effect of heparin will be avoided by using LMWHs. There is an impression that the incidence of thrombocytopenia is less with LMWHs than heparin, but to our knowledge, this has never been confirmed in a properly designed clinical study. There are reports that the administration of LMWHs can be associated with the development of thrombocytopenia both in previously unexposed individuals145 and in those with a history of heparin-induced thrombocytopenia (HIT).144 There is also evidence that LMWH preparations cross-react with plasma from patients with recent HIT.130 In contrast to the LMWHs, the Organon heparinoid, Lomoparin, which is essentially free of contaminating heparin, has minimal cross reactivity in in vitro assays for HIT226 and has been used successfully in patients with a history of HIT.150 There have, however, been rare reports of thrombocytopenia developing in patients treated with the Organon heparinoid, Lomoparin; whether these reported associations are causal or coincidental is unclear.

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