

TABLE 143-4 MANAGEMENT OF HEPARIN-INDUCED THROMBOCYTOPENIA

Stop all heparin.
 Give an alternative anticoagulant, such as lepirudin, argatroban, bivalirudin, or fondaparinux.
 Do not give platelet transfusions.
 Do not give warfarin until the platelet count returns to its baseline level. If warfarin was administered, give vitamin K to restore the INR to normal.
 Evaluate for thrombosis, particularly deep vein thrombosis.

Abbreviation: INR, international normalized ratio.

The diagnosis of HIT is established using enzyme-linked assays to detect antibodies against heparin-PF4 complexes or with platelet activation assays. Enzyme-linked assays are sensitive but can be positive in the absence of any clinical evidence of HIT. The most specific diagnostic test is the serotonin release assay. This test is performed by quantifying serotonin release when washed platelets loaded with labeled serotonin are exposed to patient serum in the absence or presence of varying concentrations of heparin. If the patient serum contains the HIT antibody, heparin addition induces platelet activation and serotonin release.

Management of HIT is outlined in **Table 143-4**. Heparin should be stopped in patients with suspected or documented HIT, and an alternative anticoagulant should be administered to prevent or treat thrombosis. The agents most often used for this indication are parenteral direct thrombin inhibitors, such as lepirudin, argatroban, or bivalirudin, or factor Xa inhibitors, such as fondaparinux.

Patients with HIT, particularly those with associated thrombosis, often have evidence of increased thrombin generation that can lead to consumption of protein C. If these patients are given warfarin without a concomitant parenteral anticoagulant to inhibit thrombin or thrombin generation, the further decrease in protein C levels induced by the vitamin K antagonist can trigger skin necrosis. To avoid this problem, patients with HIT should be treated with a direct thrombin inhibitor or fondaparinux until the platelet count returns to normal levels. At this point, low-dose warfarin therapy can be introduced, and the thrombin inhibitor can be discontinued when the anticoagulant response to warfarin has been therapeutic for at least 2 days.

Osteoporosis Treatment with therapeutic doses of heparin for >1 month can cause a reduction in bone density. This complication has been reported in up to 30% of patients given long-term heparin therapy, and symptomatic vertebral fractures occur in 2–3% of these individuals.

Heparin causes bone loss both by decreasing bone formation and by enhancing bone resorption. Thus, heparin affects the activity of both osteoblasts and osteoclasts.

Elevated levels of transaminases Therapeutic doses of heparin are frequently associated with modest elevations in the serum levels of hepatic transaminases without a concomitant increase in the level of bilirubin. The levels of transaminases rapidly return to normal when the drug is stopped. The mechanism responsible for this phenomenon is unknown.

Low-Molecular-Weight Heparin Consisting of smaller fragments of heparin, LMWH is prepared from unfractionated heparin by controlled enzymatic or chemical depolymerization. The mean molecular weight of LMWH is about 5000, one-third the mean molecular weight of unfractionated heparin. LMWH has advantages over heparin (**Table 143-5**) and has replaced heparin for most indications.

MECHANISM OF ACTION Like heparin, LMWH exerts its anticoagulant activity by activating antithrombin. With a mean molecular weight of 5000, which corresponds to about 17 saccharide units, at least half of the pentasaccharide-containing chains of LMWH are too short to bridge thrombin to antithrombin (Fig. 143-5). However, these chains retain the capacity to accelerate factor Xa inhibition by antithrombin because this activity is largely the result of the conformational changes in antithrombin evoked by pentasaccharide binding. Consequently, LMWH catalyzes factor Xa inhibition by antithrombin more than

TABLE 143-5 ADVANTAGES OF LMWH OVER HEPARIN

Advantage	Consequence
Better bioavailability and longer half-life after subcutaneous injection	Can be given subcutaneously once or twice daily for both prophylaxis and treatment
Dose-independent clearance	Simplified dosing
Predictable anticoagulant response	Coagulation monitoring is unnecessary in most patients
Lower risk of heparin-induced thrombocytopenia	Safer than heparin for short- or long-term administration
Lower risk of osteoporosis	Safer than heparin for extended administration

Abbreviation: LMWH, low-molecular-weight heparin.

thrombin inhibition. Depending on their unique molecular weight distributions, LMWH preparations have anti-factor Xa to anti-factor IIa ratios ranging from 2:1 to 4:1.

PHARMACOLOGY Although usually given SC, LMWH also can be administered IV if a rapid anticoagulant response is needed. LMWH has pharmacokinetic advantages over heparin. These advantages reflect the fact that shorter heparin chains bind less avidly to endothelial cells, macrophages, and heparin-binding plasma proteins. Reduced binding to endothelial cells and macrophages eliminates the rapid, dose-dependent, and saturable mechanism of clearance that is a characteristic of unfractionated heparin. Instead, the clearance of LMWH is dose-independent and its plasma half-life is longer. Based on measurement of anti-factor Xa levels, LMWH has a plasma half-life of ~4 h. LMWH is cleared almost exclusively by the kidneys, and the drug can accumulate in patients with renal insufficiency.

LMWH exhibits about 90% bioavailability after SC injection. Because LMWH binds less avidly to heparin-binding proteins in plasma than heparin, LMWH produces a more predictable dose response, and resistance to LMWH is rare. With a longer half-life and more predictable anticoagulant response, LMWH can be given SC once or twice daily without coagulation monitoring, even when the drug is given in treatment doses. These properties render LMWH more convenient than unfractionated heparin. Capitalizing on this feature, studies in patients with venous thromboembolism have shown that home treatment with LMWH is as effective and safe as in-hospital treatment with continuous IV infusions of heparin. Outpatient treatment with LMWH streamlines care, reduces health care costs, and increases patient satisfaction.

MONITORING In the majority of patients, LMWH does not require coagulation monitoring. If monitoring is necessary, anti-factor Xa levels must be measured because most LMWH preparations have little effect on the aPTT. Therapeutic anti-factor Xa levels with LMWH range from 0.5 to 1.2 units/mL when measured 3–4 h after drug administration. When LMWH is given in prophylactic doses, peak anti-factor Xa levels of 0.2–0.5 units/mL are desirable.

Indications for LMWH monitoring include renal insufficiency and obesity. LMWH monitoring in patients with a creatinine clearance of ≤50 mL/min is advisable to ensure that there is no drug accumulation. Although weight-adjusted LMWH dosing appears to produce therapeutic anti-factor Xa levels in patients who are overweight, this approach has not been extensively evaluated in those with morbid obesity. It may also be advisable to monitor the anticoagulant activity of LMWH during pregnancy because dose requirements can change, particularly in the third trimester. Monitoring should also be considered in high-risk settings, such as in patients with mechanical heart valves who are given LMWH for prevention of valve thrombosis, and when LMWH is used in treatment doses in infants or children.

DOSING The doses of LMWH recommended for prophylaxis or treatment vary depending on the LMWH preparation. For prophylaxis, once-daily SC doses of 4000–5000 units are often used, whereas doses of 2500–3000 units are given when the drug is administered twice daily. For treatment of venous thromboembolism, a dose of