

Current Issues in Heparin Dosing

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Unfractionated heparin (UFH) is a widely used anticoagulant, commonly given for prophylaxis and treatment of thrombotic disorders including venous and pulmonary embolism. About half of all patients with acute venous thromboembolism (VTE) are treated with UFH, despite alternatives such as low-molecular-weight heparin (LMWH).^[1] Because UFH has a narrow therapeutic window and may cause bleeding complications, aggressive monitoring is necessary to ensure efficacy and patient safety. For these reasons, the Institute for Safe Medication Practices (ISMP) placed heparin on a list of high-alert medications.^[2] This article will review key points in heparin dosing and monitoring for the adult patient; clinical scenarios will address issues in heparin dosing.

Overview of Unfractionated Heparin

Thrombus formation is a complex process. Once initiated by mechanisms such as vascular damage or inflammation, the coagulation cascade culminates in the development of fibrin and subsequent clot formation. UFH prevents thrombus growth and propagation. The heparin/antithrombin complex inhibits thrombin (factor IIa) and factors IXa, Xa, and XIIa; thrombin and factor Xa are the most sensitive to inhibition (see Figure). Inhibition of thrombin prevents thrombin-induced activation of coagulation factors V and VIII. Additionally, very small heparin molecules may cause inhibition of factor Xa.^[3]

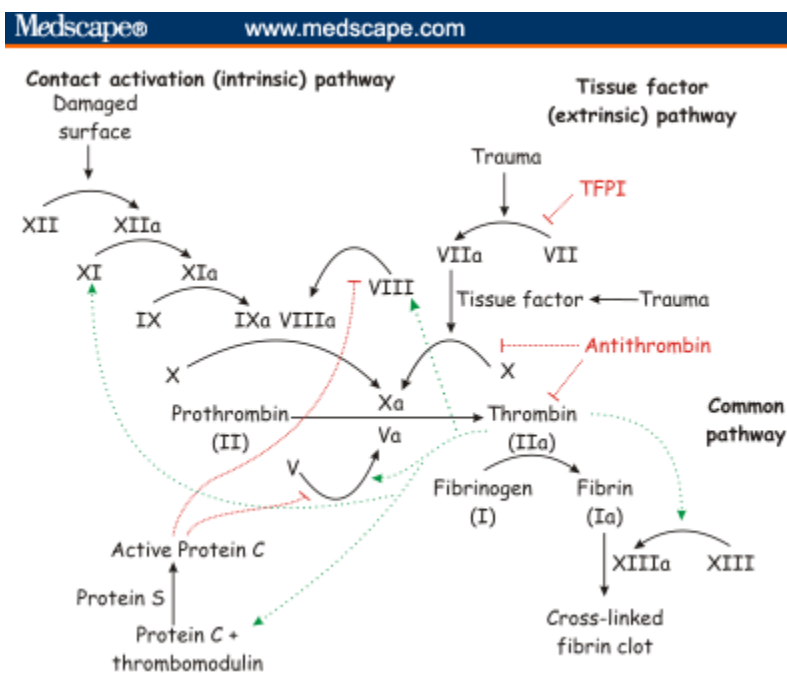


Figure 1.

Coagulation cascade.

UFH is a mixture of glycosaminoglycans of varying lengths (mean 15,000 daltons; range 3000-30,000 daltons). This heterogeneity results in variable anticoagulant activity and pharmacokinetics. In fact, only about one third of a therapeutic heparin dose is responsible for its therapeutic effects. Furthermore, higher-molecular-weight chains are eliminated faster from the circulation than lower-molecular-weight chains.^[4]

Subcutaneous bioavailability of UFH is dose-dependent, with anticoagulant onset 1-2 hours after administration. Therefore, intravenous infusions are preferred when rapid anticoagulation is necessary. The volume of distribution of UFH is 60 mL/kg, which is similar to blood volume.^[3]

The half-life of UFH is also dose-dependent and may range from 30 to 90 minutes or more in patients receiving high doses.^[3] Heparin clearance consists of a rapid saturable phase and slower first-order process. In the saturable phase, endothelial cells and macrophages bind with heparin, eliminating it from the circulation. Renal elimination constitutes most of the nonsaturable phase. Therefore, a disproportionate anticoagulant response may occur at therapeutic doses with the duration and intensity of anticoagulation rising nonlinearly with increasing dose.^[4]

Heparin Toxicity

The main toxicity of heparin is hemorrhage, which can cause serious morbidity and mortality. Major bleeding occurred in 4% of VTE patients receiving UFH who were evaluated in routine clinical practice.^[5] [Table 1](#) lists factors that may increase bleeding risk associated with UFH. Treatment of severe bleeding may require supportive care, transfusion, or the antiheparin agent protamine.^[4]

Heparin-induced thrombocytopenia type 2 (HIT) is a thrombocytopenia of 50% or more during treatment with a heparin product. HIT occurs in up to 5% of patients receiving a heparin product, usually 5-10 days after heparin initiation. The major sequelae of HIT are development of serious venous or arterial thrombosis or both. When this occurs, immediate discontinuation of UFH/LMWH is prudent, and an alternative anticoagulant must be started.^[6]

In addition, heparin-induced osteopenia may occur as a result of long-term heparin anticoagulation. The cause may be suppressed osteoblastic bone formation and activated osteoclastic bone resorption.^[7]

Heparin Dosing

Due to the many different UFH dosing guidelines, the indication is of utmost importance when determining the appropriate dose. Medical record review may help the clinician elucidate the indication, comorbidities, potential drug interactions (eg, LMWH given in emergency room), and whether the patient will need procedures (eg, percutaneous coronary intervention).

Historically, UFH dosing in standard care generally consisted of a 5000-unit bolus given intravenously with a subsequent infusion of 1000 units/hour. Raschke and colleagues^[8] described a weight-based dosing protocol of 80 units/kg IV bolus with 18 units/kg/hour infusion. This regimen was found to be safe and more efficacious compared with standard dosing. This protocol, or other similar ones, have since been implemented by many institutions.

The American College of Chest Physicians (ACCP) recommends weight-based dosing of UFH.^[4] Recommended dosing strategies are described in [Table 2](#) for specific indications. In addition, the American College of Cardiology and American Heart Association (ACC/AHA) recommend that nomograms or protocols be used for UFH management.^[9]

Various patient factors may affect response to heparin as well. In an evaluation of patients with acute coronary syndromes, longer activated partial thromboplastin times (aPTTs) were associated with weight < 70 kg, age 65 years and older, female sex, and black race; shorter aPTTs were associated with diabetes and smoking.^[10] The clinician may consider such factors when dosing UFH.

Heparin Monitoring

Heparin is usually monitored according to the aPTT, a measure of activity of fibrinogen, prothrombin, and factors V, VIII, IX, X, XI, and XII, as well as heparin inhibition of these factors.^[11] The aPTT is affected by biologic variables (eg, patient comorbidities, hemostatic defects), preanalytic variables (eg, timing of aPTT blood sample, sample storage), and analytic variables (eg, reagent sensitivity, laboratory methods).^[11]

The general use of a fixed aPTT range is not recommended.^[4] The ACCP and the American College of Pathologists recommend that the therapeutic aPTT range be calibrated for each reagent lot/coagulometer by determining the aPTT values that coincide with therapeutic heparin levels.^[4,12] For VTE treatment, the recommended antifactor Xa activity range is 0.3-0.7 IU/mL. While the range for coronary indications is uncertain, the upper range is likely 0.6 IU/mL.^[4]

The aPTT should be drawn 6 hours after initiation of UFH and 6 hours after each dose adjustment. The aPTT can be drawn every 24 hours after 2 consecutive aPTTs are therapeutic, with dosage adjustment if necessary.^[9]

Other tests may be used to monitor UFH. The activated clotting time (ACT) is a blood test used to monitor UFH when high doses are given during procedures such as percutaneous coronary intervention (PCI) or open heart surgery. UFH may also be monitored by antifactor Xa or antifactor IIa activity of heparin.^[11]

Platelets, aPTT, and hemoglobin/hematocrit should be drawn before UFH administration. During UFH therapy, monitoring of hemoglobin/hematocrit and platelet values is recommended daily at a minimum. Any significant bleeding, change in clinical condition, or change in hemodynamic stability of the patient warrants an immediate hemoglobin/hematocrit determination, platelet count, and aPTT, with dose adjustment if needed.^[9]

Clinical Scenarios

UFH Dosing via Subcutaneous Injection

Recently, the utility of therapeutic UFH dosing via subcutaneous injection for VTE treatment was revisited. The Fixed-Dose Heparin (FIDO) study was a randomized, open-label trial evaluating 345 patients who received subcutaneous UFH with an initial dose of 333 units/kg followed by a fixed-dose of 250 units/kg every 12 hours.^[13] In the control group, 352 patients received enoxaparin or dalteparin 100 IU/kg subcutaneously every 12 hours. Coagulation tests (ie, aPTT and heparin levels) were not measured.

Patients were started on warfarin for long-term anticoagulation, with discontinuation of UFH or LMWH after the international normalized ratio (INR) values were greater than 2.0 for at least 2 consecutive days. Patients were assessed at 3 days, 1 month, and 3 months after study initiation. The incidence of major and minor bleeding was not significantly different between the 2 groups at 10 days or at 3 months. Recurrent VTE was similar in both groups (UFH 3.8%, LMWH 3.4%). The authors concluded that fixed-dose subcutaneous heparin was as safe and effective as LMWH for VTE treatment.^[13]

At this time, first-line subcutaneous UFH is not recommended in lieu of IV UFH or LMWH for treatment of VTE. However, subcutaneous UFH may provide an alternative for patients with cost constraints, IV access difficulty, or renal insufficiency.^[14,15] While not routine, clinicians should be aware of this possible

dosing strategy of UFH.

UFH Monitoring for Patients With Heparin Resistance

Patients requiring unusually high doses of UFH (> 35,000 units daily) in order to maintain a desired aPTT are considered to have heparin resistance.^[4,16] Mechanisms of heparin resistance are proposed in [Table 3](#)

Management is based largely on a trial by Levine and colleagues.^[17] Patients who required 35,000 units or more of UFH by continuous infusion were randomized for monitoring by antifactor Xa levels (target 0.35-0.67 U/mL) or by the aPTT (target 60-85 seconds). Ranges were equal to a heparin level of 0.2 to 0.4 U/mL by protamine titration.

The authors found that dosing guided by antifactor Xa concentrations resulted in less heparin being administered. The incidence of recurrent VTE and bleeding events were similar between the 2 groups.^[17] Therefore, patients with heparin resistance should not be monitored by the aPTT. Instead, patients should be monitored by the heparin antifactor Xa concentration, with a desired range of 0.35-0.7 IU/mL.^[4]

UFH Monitoring in Patients With Renal Insufficiency

Thorevska and colleagues^[18] studied 331 patients with an estimated glomerular filtration rate of less than 60 mL/minute who received UFH for a wide range of indications. Patients receiving UFH had a major or minor bleeding episode incidence rate of 65.4 per 1000 person-days of anticoagulant therapy.

The authors found that female sex, extended duration, and worsening renal function were determinants of increased risk for bleeding complications. The bleeding rate in patients with renal insufficiency receiving UFH or LMWH was about 6 times greater compared with patients without renal insufficiency in an ESSENCE and TIMI 11B subgroup analysis.^[19]

The clinician should be aware of the increased bleeding risk when dosing UFH in patients with renal insufficiency. The aPTT should be monitored aggressively and the patient should be evaluated closely for signs and symptoms of bleeding.

UFH Dosing in Obese Patients

The appropriate method for dosing UFH in patients who are obese is controversial. Yee and Norton^[20] described a dosing protocol in which patients over 10 kg above ideal body weight received a heparin dose based on a dosing weight (DW) calculation. Actual body weight (ABW) was used to calculate the dose for all other patients. They found that the mean value of the first aPTT was significantly lower in the obese patients dosed by DW compared with the nonobese patients dosed by ABW. They recommended using ABW but capping the bolus and infusion rate in order to prevent overdose.

The ESSENCE and TIMI 11B subgroup analysis found that obese patients who received UFH had no difference in major hemorrhage or other clinical endpoints compared with nonobese patients.^[19] Other studies,^[21,22] albeit small, have had similar results. In their review of VTE treatment in special populations, Rondina and colleagues^[16] recommended using ABW for dosing UFH in obese patients.

The clinician should verify the indication of UFH when dosing the obese patient. Some recommendations may guide dosing in the obese patient. For example, the ACC/AHA recommends capping the initial UFH bolus and infusion in patients with ACS.^[9] (See [Table 2](#))

UFH Management in Cardiac Patients Receiving Glycoprotein IIb/IIIa Inhibitors

The initial treatment of patients with acute coronary syndromes includes aspirin and/or clopidogrel, anticoagulation with UFH or LMWH, and an intravenous platelet glycoprotein IIb/IIIa (GPIIb/IIIa) receptor inhibitor (eg, abciximab, eptifibatide, or tirofiban).^[9] The latter agents inhibit the final common pathway of platelet aggregation.^[23] Due to risk of patient safety if given improperly, this medication class joins UFH as an ISMP high-alert medication.^[2]

Initiation of the GPIIb/IIIa inhibitor may occur in the emergency room, coronary care unit, or in the cardiac catheterization laboratory. During PCI, UFH is given by intravenous bolus, and the ACT is used to guide further dosing. Coadministration of GPIIb/IIIa inhibitors with UFH during this procedure decreases thrombotic events, but at a cost of increased bleeding risk.

The EPIC trial found a 14% incidence of major bleeding in patients given concomitant abciximab and standard-dose heparin during PCI, compared with 7% in patients receiving only UFH.^[24] The EPILOG trial studied comparisons between standard weight-based UFH (100 units/kg bolus, max 10,000 units; additional boluses to maintain target ACT 300 seconds) and placebo; between standard weight-based UFH and abciximab; and between low-dose, weight-based UFH (70 units/kg, max 7000 units; additional boluses to maintain ACT 200 seconds) and abciximab. The addition of abciximab to UFH decreased the 30-day endpoint of a composite measure of death, myocardial infarction, or revascularization. The low-dose UFH group had fewer bleeding complications without an increase in thrombotic events.^[25]

Largely as a result of the EPILOG trial, decreased dosing of UFH has become standard of care during PCI with GPIIb/IIIa inhibitor use.^[23] When bolus UFH is given in combination with a GPIIb/IIIa inhibitor during PCI, the recommended dose is 50-70 units/kg, with a target ACT of greater than 200 seconds.^[23]

To date, no clinical guidelines exist for the dosing of concomitant UFH and GPIIb/IIIa inhibitors outside the cardiac catheterization laboratory, such as in the emergency room or coronary care unit. When UFH is used instead of LMWH, the size of the bolus dose may be based on whether and when angiography is planned.

In the ACUTY trial, UFH given with a GPIIb/IIIa inhibitor was dosed as a 60-units/kg bolus with 12 units/kg/hour infusion for an aPTT of 50-75 seconds before angiography; additional UFH boluses were given during PCI to maintain an ACT between 200-250 seconds.^[26] In the SYNERGY trial, UFH given with a GPIIb/IIIa inhibitor was dosed as a 60 units/kg (max 5000 units) bolus with 12 units/kg/hour (up to 1000 units/hour initially), with a goal aPTT 1.5-2 times control or 50-70 seconds prior to catheterization. Additional UFH boluses were given during PCI if it was necessary to achieve an ACT lower than 250 seconds.^[27]

Although these trials were not designed to study optimal UFH dosing and monitoring with concomitant GPIIb/IIIa administration, clinicians may use the protocols to guide their dosing strategies.

In order to prevent the increased bleeding risk associated with concomitant GPIIb/IIIa inhibitor use and UFH, the clinician should verify whether the ACS patient is to receive a GPIIb/IIIa inhibitor. Dosing of UFH should then be confirmed by the physician and/or institution guidelines.

Conclusion

UFH continues to be a cornerstone of treatment for a range of indications requiring anticoagulation. Careful dosing and monitoring are necessary to reduce the risk for patient harm and to maximize the therapeutic benefit. The clinician should refer to UFH guidelines whenever possible to assist in dosing and monitoring of this complex medication. (See [Table 4](#))

Table 1. Factors That May Increase Bleeding Risk in UFH Use^[4]

Dose
Coadministration of thrombolytic
Coadministration of glycoprotein IIb/IIIa inhibitor
Recent surgery, trauma, or invasive procedure
Concurrent hemostatic defects

Table 2. UFH Dosing for Special Patient Groups^[4]

Indication	Recommended Dosage
VTE ^a	80 units/kg bolus; 18 units/kg/h infusion
ACS ^b	60-70 units/kg bolus (max 5000 units); 12-15 units/kg/h (max 1000 units/h) infusion
Acute STEMI ^c with rtPA ^d	60 units/kg bolus (max 4000 units); 12 units/kg/h (max 1000 units/h) infusion

a. venous thromboembolism; b. acute coronary syndromes; c. ST-segment elevation myocardial infarction; d. recombinant tissue plasminogen activator

Table 3. Potential Causes of Heparin Resistance^[4]

Antithrombin deficiency
Increased heparin clearance
Increased number of heparin-binding proteins
Increased factor VIII levels
Increased fibrinogen levels
Drug-induced resistance

Table 4. Guidelines for Heparin Dosing and Monitoring

The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy ^[28]
ACC/AHA 2002 Guideline Update for the Management of Patients With Unstable Angina and Non-ST-

Segment Elevation Myocardial Infarction ^[9]
ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation ^[29]
ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease ^[30]
ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention ^[31]
ESC Guidelines for Percutaneous Coronary Interventions ^[32]
College of American Pathologists Conference XXXI on Laboratory Monitoring of Anticoagulant Therapy: Laboratory Monitoring of Unfractionated Heparin Therapy ^[12]

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