Chapter 11

Heparin, Low Molecular Weight Heparin, and Fondaparinux

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Chapter Outline

Introduction

Historically, unfractionated heparin (UFH) represented the mainstay parenteral anticoagulant used in the prevention or treatment of arterial and venous thrombosis. In recent years, agents with improved pharmacologic properties such as the low molecular weight heparins (LMWHs) and the pentasaccharide (fondaparinux) have been added to the armamentarium of antithrombotic agents used for these indications.[1,2] Pharmacists and health-care providers involved in managing antithrombotic therapies need to be familiar with the pharmacologic and pharmacokinetic differences between these agents, and also with the variety of clinical nuances for appropriate and safe use.

The goal of this chapter is to provide a practical overview on essential clinical knowledge that will facilitate appropriate and safe use of UFH, LMWH, and fondaparinux in daily clinical practice.

Unfractionated Heparin

Unfractionated heparin has been one of the most commonly used anticoagulants for the prevention and treatment of thrombosis. Commercially available UFH preparations are isolated from porcine intestinal mucosa or bovine lung. Bovine derived heparin, however, is no longer available in the United States. No differences in antithrombotic activity have been demonstrated between the various UFH preparations.[1,3,4]

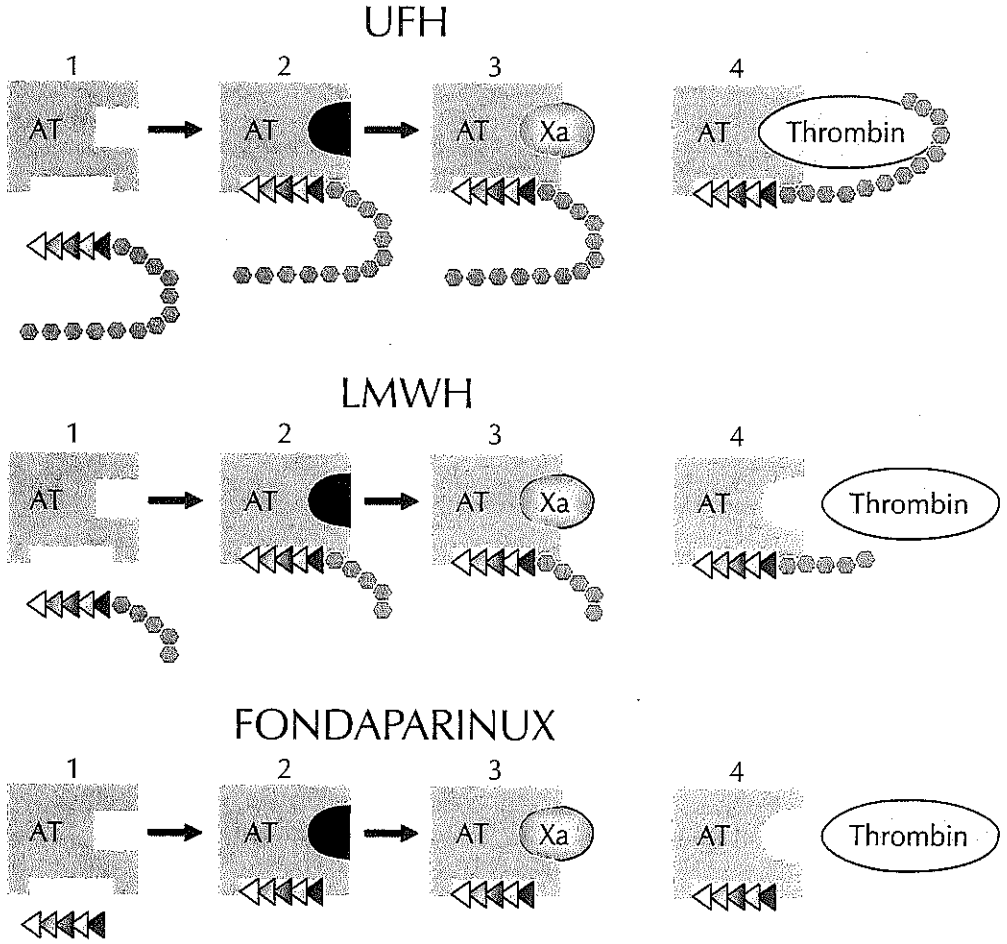


Figure 11-1. Mechanism of action of UFH, LMWH, and fondaparinux. Abbreviations: UFH = unfractionated heparin; LMWH = low molecular weight heparin; AT = antithrombin; Xa = activated factor X.

Pharmacology

Heparin is composed of a heterogeneous mixture of glycosaminoglycans with variable chain lengths and pharmacological properties. The mean molecular weight of UFH is 15,000 daltons (range of 3,000 to 30,000 daltons). The length of each UFH molecule confers its anticoagulant and elimination profile. Longer UFH chains are cleared more rapidly, generally by hepatic elimination than shorter chains which tend to be cleared renally.[1, 5]

Heparin exerts its anticoagulant effect by augmenting the natural anticoagulant antithrombin (AT) (see Figure 11-1).[1] A specific pentasaccharide sequence on the heparin molecule binds to AT and causes a conformational change which greatly accelerates its enzymatic activity. This complex inhibits thrombin (factor IIa) as well as factors Xa, IXa, XIa, and XIIa. Thrombin and factor Xa are most sensitive to this inhibition and are inactivated in an equal 1:1 ratio. In order to inactivate thrombin, the UFH molecule needs to form a ternary complex by binding to both AT and thrombin. Only UFH molecules that are at least 18 saccharide units long are able to form this bridge between AT and thrombin. In contrast, inhibition of factor-Xa does not require the formation of a ternary complex. Heparin molecules as short as 5 saccharide units can catalyze the inactivation of factor-Xa. Unlike thrombolytics, UFH will not dissolve a formed clot but prevent its propagation and growth.[1, 3, 5, 6]

After it has produced its effect, UFH detaches from AT and re-attaches with another AT molecule. Because of its large size, the UFH-AT complex is unable to inactivate clot-bound thrombin or factor Xa. UFH binds to platelets and has an inhibitory effect on platelet aggregation. In addition, when used in higher doses, UFH also binds to heparin cofactor II, further enhancing the inhibition of thrombin activity.[1, 5, 6]

Clinical Pearl

Patients with acute thrombosis may frequently have higher UFH dose requirements to attain therapeutic effect as these patients have been noted to eliminate UFH more rapidly, possibly because of increased binding to acute phase reactants.

Pharmacokinetics/Pharmacodynamics

The half-life of UFH is dose-dependent. The typical half-life ranges between 30 to 90 minutes, but it can be longer (~150 minutes) when UFH is given in high doses (see Table 11-1). Unfractionated heparin is eliminated by two mechanisms: (1) enzymatic degradation via a rapid, saturable zero-order process, and (2) renally via a first-order, non-saturable slower process. At lower concentrations, UFH is primarily cleared via enzymatic processes while at higher concentrations it may be subject to renal elimination. The contribution of each mechanism to the total clearance of UFH is related to the dose and size of the heparin molecules. The rate of clearance of UFH is reduced in patients with renal and hepatic dysfunction.[1, 5-7]

Due to its nonspecific binding to various cellular proteins, UFH has several limitations including poor bioavailability when given subcutaneously (SC) and significant intra- and inter-patient variability in

Clinical Pearl

Due to its lower and variable bioavailability if the SC route of administration is used, higher doses of UFH should be initiated in order to attain therapeutic anticoagulation effect quickly. The initial SC UFH dose should be approximately 10% to 20% higher than the usual IV dose required to maintain therapeutic effect (see Table 11-2).

Table 11-1. CD

Pharmacologic and Clinical Properties of UFH, LMWH, and Fondaparinux

Property	UFH	LMWH	Fondaparinux
Source	Extracted from porcine intestinal mucosa or beef lung	Chemical or enzymatic depolymerization of UFH	Chemical synthesis
Molecular weight (Daltons)	Mean 15,000	Mean 5000	1728
SC bioavailability	30% to 70% (dose dependent)	~90%	100%
Activated clotting factors reduced	Multiple: factors IIa, IXa, Xa, XIIa	Factors Xa > IIa	Factor Xa
Binding to proteins other than target	Yes	Limited	Limited
Anti-Xa:anti-IIa	1:1	2:1 to 4:1	100% anti-Xa
Primary route of elimination	Enzymatic degradation at low doses and renal at higher dose	Renal primarily	Renal
Half-life (SC route)	30–150 min (dose dependent)	3–4 hours	17–21 hours
Effects of protamine	Complete neutralization	Partial neutralization	No effect

SC = subcutaneous; UFH = unfractionated heparin; LMWH = low molecular weight heparin

anticoagulant response.[3, 8] When given via the SC route, the bioavailability of UFH ranges from 30% when given in low doses to as much as 70% when given in high doses.[1, 5]

After SC administration, the onset of anticoagulant effect is usually achieved 1 to 2 hours and peak effect is achieved at 3 hours.[9] Several days may be required to reach steady-state pharmacodynamic assessment values when SC UFH is given in full therapeutic doses. Intramuscular administration is not recommended due to erratic absorption and risk of hematoma formation. When UFH is given via the intravenous (IV) route, continuous IV infusion is preferred over intermittent IV boluses. Intermittent bolus injections result in high peak anticoagulant levels and have been associated with a higher risk of major bleeding.[1, 4, 5]

Clinical Pearl

When transitioning from UFH to an alternative parenteral anticoagulant agent with rapid onset of activity, it may be preferable to wait a selected period of time before initiating the alternative therapy. However, in the setting of multiple distractions to the health-care staff, delay in initiating the ordered anticoagulant can occur, resulting in an undesired lapse in anticoagulation therapy. Thus, unless an atypical clinical situation is present, it is suggested to stop the UFH at the same time as initiating any new anticoagulant that has a rapid onset of action (also see Table 11-3).

Indications

The use of UFH has been investigated for the prevention and treatment of thrombosis in several arterial and venous indications. The most commonly used indications for UFH include the prophylaxis and treatment of venous thromboembolism (VTE), prevention of stroke in atrial fibrillation, disseminated intravascular coagulation, prophylaxis and treatment of peripheral arterial embolism, prevention of clotting in arterial and cardiac surgeries, and as an anticoagulant in blood transfusions, extracorporeal circulation, dialysis procedures, and in blood samples for laboratory purposes.[1, 4]

Dosing and Administration

For systemic anticoagulation effects, UFH is typically administered via the IV or SC route.[1, 4] The actual dose and route of administration for UFH will be dependent on the indication for therapy, the therapeutic goals, and the patient's individual response to therapy (see Tables 11-2, 11-4, and 11-5). For the prevention of VTE, UFH is usually given by SC injection. The typical dose for prophylaxis ranges from 5,000 units given every 12 hours in moderate risk patients to 5,000 units given every 8 hours in higher risk patients.[1, 10] In order to improve compliance and to avoid missed doses, standard dosing times should be developed especially when SC UFH is given as an every 8-hour regimen. In certain clinical situations when there is a need for rapid reversal of anticoagulation, such as increased bleeding risk, or the need to rapidly reverse anticoagulation for an invasive procedure, or when there are bioavailability concerns (critical care setting)

Table 11-2. CD

Sample Dosing and Monitoring Nomogram for Adjusted-Dose Subcutaneous UFH

As an alternative to IV administration, UFH can be administered SC twice daily. The recommended initial dose is 250 units/kg SC given q12 hours (or 17,500 IU SC every 12 hours). aPTT should be drawn at 6 hours (mid-interval) after the dose. Subsequent doses should be adjusted based on aPTT response (see dosing chart below).

aPTT (sec)	Dose Adjustment	Time of Next aPTT
<40	Increase by 36 to 48 units/kg q 12 hours	6 hours post-dose
40–59	Increase by 24 to 36 units/kg q 12 hours	6 hours post-dose
60–90 (institution-specific therapeutic range)*	No change	Next AM, then daily (less frequent monitoring may be required with long-term use)
91–103	Decrease by 6 to 12 units/kg q 12 hours	6 hours post-dose
104–124	Decrease by 12 to 24 units/kg q 12 hours	6 hours post-dose
>124	Decrease by 24 to 36 units/kg q 12 hours	6 hours post-dose

*Institution specific therapeutic aPTT range of 60–90 seconds is equivalent to a plasma heparin concentration of 0.3–0.7 anti-Xa units/mL or 0.2–0.4 units/mL by protamine titration. Range may vary depending on the assay sensitivity to heparin for a particular reagent.

aPTT = activated partial thromboplastin time; IV = intravenous; SC = subcutaneous; UFH = unfractionated heparin; AM = morning.

Table 11-3. CD

Practical Considerations for Transitioning Between Various Anticoagulant Agents

Conversion from IV UFH infusion to adjusted-dose SC UFH	Calculate the 24-hour IV UFH dose requirement needed to maintain therapeutic aPTT Increase the total 24-hour UFH dose requirement by 10% to 20% (SC dosage requirements are higher then IV) Divide the dose calculated above by 2 to determine the initial q12 hours SC dosing requirement Discontinue IV UFH and initiate the 1st SC UFH dose (as calculated above) within 1 hour Check aPTT at 6-hours after 1st SC dose Adjust further SC UFH doses based on aPTT and dosing nomogram from Table 11-2
Conversion from IV UFH infusion to SC LMWH (or SC fondaparinux)	Calculate the appropriate LMWH (or fondaparinux) dose based on the specific indication for use and patient weight Discontinue IV UFH and initiate the 1st SC LMWH (or fondaparinux) dose within 1 hour
Conversion from SC LMWH or SC fondaparinux to IV UFH infusion	Calculate the appropriate IV UFH dose based on indication for use and patient weight (see Table 11-4) Discontinue SC LMWH or SC fondaparinux and initiate IV UFH 1–2 hours (no bolus) before the next SC LMWH or fondaparinux dose would have been administered: a. When switching from SC LMWH given q12 hours, initiate IV UFH at 10 to 11 hours after last LMWH dose b. When switching from SC LMWH given q24 hours, initiate IV UFH at 22 to 23 hours after last LMWH dose c. When switching from SC fondaparinux given q24 hours, initiate IV UFH at 22 to 23 hours after last fondaparinux dose d. Check patient's renal status and if impaired, the IV UFH dosing initiation intervals suggested in a–c above need to be extended accordingly Check aPTT at 6 hours after initiating the IV UFH infusion Adjust further UFH doses based on aPTT and dosing nomogram from Table 11-5
Conversion from SC LMWH or SC fondaparinux to adjusted-dose SC UFH	Calculate the adjusted-dose SC UFH dosing requirements: the recommended initial dose is 250 units/kg SC given q12 hours Discontinue SC LMWH or SC fondaparinux and initiate SC UFH at the time the next SC LMWH or fondaparinux dose is scheduled to be administered: a. When switching from SC LMWH given q12 hours, initiate SC UFH at 12 hours after last LMWH dose b. When switching from SC LMWH given q24 hours, initiate SC UFH at 24 hours after last LMWH dose c. When switching from SC fondaparinux given q24 hours, initiate SC UFH at 24 hours after last fondaparinux dose d. Check patient's renal status and if impaired, the SC UFH dosing initiation intervals suggested in a–c above need to be extended accordingly aPTT should be drawn at 6 hours (mid-interval) after the 1st SC UFH dose Subsequent SC UFH doses should be adjusted based on aPTT and dosing nomogram from Table 11-2

with the SC dose, a continuous IV UFH infusion may be considered targeting a limited (10–20 seconds) rise in the activated partial thromboplastin time (aPTT). The dose of UFH required to achieve a therapeutic anticoagulant response is correlated to the patient's weight.[11, 12] Thus, when immediate and full anticoagulation is required, a weight-based IV bolus dose followed by a continuous infusion is recommended (see Tables 11-4 and 11-5).[1, 5, 11-13] In addition to weight as a predictor for UFH dosing, recent reports support the use of dosing protocols that are based on sex, age and height.[14] Improved initial UFH heparin dosing estimations have also been reported with protocols based on patient age and plasma volume.[15]

The initial recommended weight-based UFH dose in the treatment of VTE is 80 units/kg bolus and 18 units/kg/hour infusion.[11] In the treatment of acute coronary syndromes, the recommended UFH initiation doses are usually lower then the doses used in the treatment of VTE.[1] For patients with unstable angina and non-ST-segment elevation myocardial infarction the recommended UFH bolus is 60–70 units/kg (maximum dose 5,000 units) and the infusion is 12–15 units/kg/hour (maximum dose 1,000 units/hour).[1, 16, 17] In patients with ST-elevation myocardial infarction also receiving thrombolytics, the recommended UFH bolus dose is 60 units/kg (maximum dose 4,000 units) and the infusion is 12 units/kg/hour (maximum dose 1,000 units/hour).[1, 18] In patients undergoing percutaneous coronary intervention, when UFH is administered without the use of glycoprotein IIb/IIIa inhibitors, the recommended UFH bolus dose is 70–100 units/kg, with additional boluses of 2,000–5,000 units if target activated clotting times (ACT)

Table 11-4. CD

Sample Weight-based Dosing Nomogram for IV UFH in Acute Thrombosis

Initial Loading Dose	Initial Infusion Rate
60–80 units/kg	12–18 units/kg/h
ACS: 60 units/kg (maximum 5000 units; 4000 units if concurrent GPIIbIIIa inhibitor or thrombolytic) Ischemic stroke: No bolus VTE: 80 units/kg (maximum 10,000 units)	ACS: 12 units/kg/h (maximum start rate 1,000 units/h) Ischemic stroke: 12 units/kg/h (maximum start rate 1,000 units/h) VTE: 18 units/kg/h (maximum start rate 1,500 units/h)

Abbreviations: UFH = unfractionated heparin; VTE = venous thrombosis; ACS = acute coronary syndromes; GP IIb/IIIa = glycoprotein IIb/IIIa inhibitors; h = hour; IV = intravenous.

Table 11-5. CD

Sample Monitoring Nomogram for IV UFH

aPTT (sec)	Maintenance Infusion Rate Dose Adjustment	Time of Next aPTT
Less than 35	80 units/kg bolus then increase infusion by 3 units/kg/h	6 hours
35–49	40 units/kg bolus then increase infusion by 2 units/kg/h	6 hours
50–59	No bolus. Increase infusion by 1 units/kg/h	6 hours
60–90 (institution-specific therapeutic range)*	No change	Next AM, then daily
91–103	Decrease infusion by 1 units/kg/h	6 hours
104–124	Hold infusion for 30 minutes then decrease by 2 units/kg/h	6 hours after resuming infusion
> 124	Hold infusion for 1 hour then decrease by 3 units/kg/h	6 hours after resuming infusion

*Institution specific therapeutic aPTT range of 60–90 seconds is equivalent to a plasma heparin concentration of 0.3–0.7 anti-Xa units/mL or 0.2–0.4 units/mL by protamine titration. Range may vary depending on the assay sensitivity to heparin for a particular reagent.

kg = kilograms; h = hours; AM = morning; aPTT = activated partial thromboplastin time.

Clinical Pearl

In cases of acute thrombosis, or when there is a need to rapidly establish anticoagulation, a bolus dose of UFH may be necessary. If emergent anticoagulation is not necessary, then starting the UFH infusion without a bolus dose will make it easier to assess the response to the infusion alone, titrate to the desired therapeutic effect, and minimize dosing errors (such as under adjusting the infusion rate) associated with administering a bolus dose.

are not achieved. The initial UFH bolus is reduced to 50–70 units/kg when glycoprotein IIb/IIIa inhibitors are also given.[1, 19] In selected populations, such as stroke or atrial fibrillation (non-ablation), a bolus dose may not be necessary. Policies for such selected populations should be determined in advance, and included as options in standardized ordering and monitoring protocols.

Weight-based UFH dosing regimens are more likely to exceed the therapeutic aPTT threshold in the first 24 hours after initiating treatment compared to more traditional dosing regimens such as 5,000 unit bolus dose followed by an infusion administered at 1,000 units/hour.[11] Achieving a therapeutic aPTT in the first 24 hours after initiating UFH has been shown to lower the risk of recurrent VTE.[20, 21]

The SC route of administration can also be employed when treating an acute venous thrombotic event.[1, 22, 23] If the SC route is selected for the treatment of VTE, an initial 5000 unit IV bolus should be given followed by 17,500 units given SC every 12 hours.[1, 23] Subsequent doses of SC UFH need to be adjusted based on the patient's aPTT response (see Table 11-2). However, recent data also supports the efficacy of weight based, unmonitored SC UFH (initial dose of 333 units/kg followed by 250 units/kg every 12 hours) for the treatment of acute VTE, while transitioning to warfarin over a short period of time. The use of weight-based, unmonitored SC UFH has the potential to change the paradigm of VTE treatment and anticoagulant monitoring with UFH.[24] For non-obese patients, the actual body weight should be used to calculate the initial UFH dose.[1, 5, 25] For obese patients, using the actual body weight to calculate the initial dose is controversial. Some experts recommend using an adjusted body weight or a modified dosing weight instead.[26] The infusion rate is then adjusted based on laboratory monitoring of the patient's response.

Higher UFH dose requirements have been reported in patients with acute thrombosis, AT deficiency, and elevated factor VIII levels. The requirement of these higher unfractionated heparin doses is termed *heparin resistance*, and it should be suspected in patients who require more than 35,000–40,000 units (~25 units/kg/hour) of UFH in a 24-hour period.[1, 27]

Clinical Pearl

Heparin is available in multiple strengths. To avoid potential medication errors, standardization of a bag concentration or identification of different strengths should be considered. Premixed heparin bags (25,000 units/250 mL D5W) are available to reduce potential compounding errors or delays in initiating therapy.

Clinical Pearl

Lack of a measured response to heparin at rates > 25 units/kg/hour (resistance) can occur when lower antithrombin levels (< 70%), or elevated factor VIII or fibrinogen levels are present. When heparin resistance is suspected, a non-antithrombin dependent anticoagulant agent such as a direct thrombin inhibitor can be considered as an alternative treatment option. If a LMWH is used in this setting, heparin resistance may not be recognized potentially resulting in subtherapeutic anticoagulation.

Monitoring

When used in full therapeutic doses, the administration of UFH requires frequent monitoring and subsequent dose adjustments due to intra and inter-patient variability of its anticoagulant response.[1, 28, 29] A variety of laboratory tests can be used to monitor the anticoagulant response to UFH, including the aPTT, ACT, anti-factor Xa activity, and plasma heparin concentrations measured by anti-factor-Xa inhibition or protamine titration assays.[1, 5, 30]

Despite its limitations, the aPTT is still the most widely used laboratory test in clinical practice to monitor the anticoagulant response to UFH. Historically, the therapeutic range of aPTT was con-

Clinical Pearl

Any time new reagents are purchased for determining the aPTT, the laboratory will need to recalibrate the aPTT target range. If a significant change in the sensitivity for a reagent batch occurs, there may be a notable change in the reported aPTT target ranges, which may be different than the ones listed on pre-established dosing and monitoring protocols. A process should be in place at each institution where any changes in the aPTT reagents are evaluated, and any necessary alteration in the therapeutic range is coordinated with all current heparin dosing protocols in advance of the reagent change.

sidered appropriate if maintained between 1.5 to 2.5 times the mean normal control value. However, due to variations in the reagents and instruments used to measure the aPTT in different laboratories, many reagents do not accurately measure the response to UFH within this fixed therapeutic range. Thus, each institution should establish its own specific therapeutic aPTT range for UFH calibrated for each instrument and reagent lot. This institution-specific aPTT therapeutic range needs to be correlated with a plasma heparin concentration of 0.3 to 0.7 units/mL by an amidolytic anti-factor Xa assay or with a plasma heparin concentration of 0.2 to 0.4 units/mL by protamine titration for the treatment of VTE. The exact therapeutic range for patients with acute coronary syndromes is not well established but it has been suggested at an upper limit of 0.6 units/mL.[1, 31]

The aPTT should be obtained at baseline, 6 hours after initiating the UFH infusion, and 6 hours after each dose change as this is the time required to reach steady-state. The UFH dose is then adjusted based on the specific aPTT measurement and the institutional-specific designated therapeutic range (see Table 11-5).[1, 30, 31]

When interpreting a given aPTT value, it is important to verify that the infusion rate was correct, and that there were no recent interruptions in the UFH infusion. It should also be noted that as the INR increases during concurrent warfarin therapy initiation, a corresponding rise in the aPTT may occur independent of any alterations in the heparin infusion. When "heparin resistance" is suspected, the use of anti-factor Xa concentrations by an assay process that does not incorporate the addition of AT may be an alternative option to the aPTT for UFH monitoring. In addition, the aPTT is not suitable to monitor heparin therapy in patients requiring doses of heparin that will produce serum concentrations > 1 unit/mL. The ACT is the recommended assay when high doses of heparin are used especially during coronary angioplasty or coronary bypass surgery.[1, 19, 27]

Clinical Pearl

Checking aPTT values earlier than 6 hours after initiating the UFH infusion may be considered, in order to determine if an adequate infusion rate is present (aPTT value close to baseline.) When interpreting this "early" aPTT value, it has to be noted that the bolus dose may artificially increase this reading. UFH bolus doses of > 5000 units can also have an effect on aPTT values drawn 8 hours later.

Clinical Pearl

In selected surgical procedures such as coronary bypass surgery, vascular surgery, extra corporeal membranous oxygenation (ECMO) or coronary interventions, higher amounts of UFH and ACT monitoring may be used. If the UFH is continued post procedure, it is important to confirm that the rate was appropriately reduced. Any subsequent aPTT measurements, if no reversal was used, may still be influenced by the higher infusion for 8 hours or so after adjusting the infusion rate downwards.

Several studies have demonstrated that the anti-factor Xa assay can be successfully used instead of the aPTT for UFH anticoagulant effect and dosage monitoring.[14, 15, 27] Levine et al. reported that heparin levels by protamine titration of 0.2 to 0.4 units/mL were equivalent to chromogenic heparin anti-factor Xa levels of 0.35 to 0.67 units/mL.[27] As some institutions have been transitioning to this alternative monitoring parameter for UFH, great care should be taken as recent reports showed variations in the equivalency between heparin levels by protamine titration and levels by anti-factor Xa activity that are instrument and laboratory assay dependent.[32-35] In one study, the average chromogenic anti-factor Xa levels that were equivalent to a

heparin level of 0.2 units/mL and 0.4 units/mL by protamine sulfate titration were 0.27 units/mL and 0.44 units/mL[33] which is different than the ranges reported by Levine et al.[27] Significant differences in heparin anti-factor Xa levels were also reported when heparin levels were compared between different instruments and between different commercially available assays, suggesting that the therapeutic range for heparin anti-factor Xa analysis may need to be specific for the specific instrument and laboratory assay used.[35] In addition, adjusting UFH doses based on measured anti-Xa activity has not been validated nor correlated to improved clinical outcomes. More so, the anti-Xa activity assays may not measure some of the other anticoagulant effects of heparin.

Side Effects, Precautions, and Contraindications

Similar to other anticoagulant agents, bleeding is the most commonly associated side effect with UFH. The incidence of UFH associated bleeding complications is minimal with SC prophylactic doses, but higher (2% to 4%) with treatment doses given via IV infusion.[1, 5, 36, 37] The incidence of UFH associated bleeding increases with concurrent use of thrombolytics, glycoprotein IIb-IIIa inhibitors, and other antithrombotic agents. In addition, higher UFH doses have been linked to increased bleeding complications. The risk of UFH-induced bleeding is also increased in surgical or trauma patients, elderly, after invasive procedures, in patients with thrombocytopenia, heavy alcohol consumption, renal failure, neoplasms, and in cases where there is a pre-existing source of bleeding.[1, 4, 5, 37, 38] Patients receiving UFH should be closely monitored for signs and symptoms of bleeding complications. Symptoms will vary depending on the location of bleeding, and may include joint pain, chest pain, abdominal pain, severe headache, black tarry stools, blunt hematuria, and the passage of bright red blood per rectum. In cases of major bleeding complications, therapy should be stopped immediately and appropriate treatment and reversal measures provided. Minor bleeding complications include bruising, epistaxis, gingival bleeding, and prolonged bleeding from cuts.[4-6, 37] Interestingly, the evidence of linking elevated aPTT results and the risk of bleeding in patients treated with UFH is weak at best.[1, 19] As the risk of bleeding is closely related to the presence of underlying risk factors, before initiation of therapy, patients should be carefully screened for any contraindications to UFH.

Local irritation, pain at the injection site, erythema, histamine-like reactions (most commonly itching and burning on plantar side of the feet) and hematoma has been associated with SC UFH administration.[1, 4, 5, 8] In addition, hypersensitivity reactions with chills, fever, and urticaria have also been associated with UFH therapy.[4]

Alopecia, priapism, hyperkalemia, elevated ALT/AST levels, and osteoporosis have been reported with long-term use of UFH.[1, 4-6, 38] Drug interactions are limited with UFH, however, care should be used when given concurrently with other antithrombotic agents due to the increased potential for bleeding complications. Digitalis, nicotine, and antihistamines may counteract the anticoagulant effect of UFH.[4]

Heparin-associated thrombocytopenia (HAT) is a benign, transient, and mild non-immune mediated phenomena, generally occurring within the first few days of treatment in the heparin naïve patient. Platelet counts rarely drop below 100,000 in patients with HAT and recover with continued therapy. In contrast, heparin-induced thrombocytopenia (HIT) is a rare but extremely severe immune-mediated, drug-induced complication associated with UFH use. Once HIT is diagnosed or strongly suspected, prompt discontinuation of all heparin sources (including heparin flushes) and initiation of an alternative anticoagulant therapy is imperative.[39-41]

Clinical Pearl

Patients with pork allergy cannot be treated with UFH derived from pork intestines. Fondaparinux, a factor-Xa inhibitor that is a synthetic molecule, can be used as an alternative therapeutic approach in patients with pork allergy and also patients who develop an allergic reaction from either UFH or an LMWH.

Clinical Pearl

In patients with HIT who are managed only by discontinuation of UFH, the risk of symptomatic thrombosis is 25% to 50%, and fatal thrombosis is 5%. Thus, in cases where there is a strong clinical suspicion of HIT, in addition to stopping UFH immediately, a direct thrombin inhibitor should be initiated even while waiting for laboratory confirmation for the diagnosis.

The drugs of choice for the treatment of HIT with or without thrombosis are the direct-thrombin inhibitors (DTIs; refer to Chapter 10 for more information on DTIs). Future use of UFH, especially within 3 to 6 months following the diagnosis of HIT, should be avoided. As PF4-heparin antibodies are transient and usually cleared within 3 months, patients with a history of HIT should be tested for HIT antibodies prior to any future use of UFH. Although there are limited data regarding the use of UFH in patients with a remote history of HIT, these patients should receive alternative anticoagulant agents for most indications until more rigorous data will be available.[42, 43]

In cases of typical-onset HIT, platelet counts begin to fall 5 to 10 days after exposure to UFH in heparin naïve individuals, and reach a threshold by days 7 to 14. In delayed-onset HIT, the development of thrombocytopenia can be delayed up to 20 to 40 days, and begin several days after heparin has been stopped in patients naive to heparin therapy. In contrast, rapid-onset HIT can occur very quickly (within 24 hours following UFH initiation), especially in patients with a recent exposure to heparin (i.e., previous 3 months).[40, 42, 44]

Platelet counts less then 150,000 mm^3 or a drop in platelet count greater than 50% from baseline is considered indicative of HIT. In addition to clinical findings, the diagnosis of HIT must be supplemented by laboratory tests confirming the presence of antibodies to heparin or platelet activation induced by heparin. Thrombosis development shortly after documenting thrombocytopenia is a characteristic finding in almost half of all the patients with HIT. Platelet count monitoring should be performed in patients receiving UFH. Before treatment is initiated a baseline platelet count should be documented, then followed by monitoring of platelet counts every other day for 14 days or until UFH therapy is discontinued, whichever occurs first.[40, 42, 43] If HIT occurs, it is crucial to document the occurrence of this reaction in the patient's medical record and educate the patient on this adverse effect so that future heparin use may be appropriately avoided.

Clinical Pearl

Delayed onset HIT has been reported with the use of heparin (UFH and LMWH.) In individuals who have been recently exposed to heparin and present with a new thrombotic event, a platelet count should be immediately done to assess the presence of HIT prior to initiating any form of heparin.

Clinical Pearl

In some patients with documented HIT, the platelet count will drop 50% or more from the baseline value, but may not necessarily be less then 150,000. It is important to recognize this > 50% drop in platelet count as indicative of HIT. Development of thrombosis may occur well before the laboratory diagnosis of HIT is made. Thus, acute thrombosis in any patient receiving heparin therapy should be a red flag and these patients should be immediately evaluated for the presence of HIT.

Low Molecular Weight Heparin

Developed in the 1980s, the LMWHs are smaller molecular weight fragments obtained by chemical or enzymatic depolymerization techniques of UFH.[1, 29] Three LMWH products are commercially available in the U.S.: dalteparin, enoxaparin, and tinzaparin. LMWHs are composed of a heterogeneous mixture of glycosaminoglycans, and vary slightly in their molecular weight distributions and pharmacologic properties (Table 11-1). LMWHs have improved pharmacodynamic and pharmacokinetic properties in comparison to UFH.[1, 6] The introduction of the LMWHs had a significant impact on how we administer anticoagulant therapy, particularly in the acute phase. Due to their convenience of use, these agents have been replacing the use of UFH in many clinical situations.

Pharmacology

Similar to UFH, LMWHs preclude the propagation and extension of formed thrombi.[1] Their anticoagulant effect is mediated through a specific pentasaccharide sequence that binds to AT and potentiates its activity. The smaller molecular weight (< 18 saccharide units in length) fragments cannot bind AT and thrombin simultaneously (see Figure 11-1). Less than 50% of the LMWH molecules have the 18 saccharide units chain length required for simultaneous binding of antithrombin and thrombin. Thus, LMWHs are more specific to inhibiting factor Xa than for inhibiting the activity of thrombin (factor IIa). Their anti-factor Xa:IIa activity ratio, which can vary between agents, ranges from 2:1 to approximately 4:1. In contrast, UFH has an antifactor Xa:IIa activity ratio of 1:1 (Table 11-1).[1, 3, 6, 45]

Clinical Pearl

The aPTT test is not an appropriate laboratory parameter to measure the effect of LMWH. LMWH have minimal effect on factor IIa, thus limited prolongation of aPTT may only be seen in cases of LMWH overdoses.

Pharmacokinetics/Pharmacodynamics

LMWHs have potentially desirable pharmacodynamic and pharmacokinetic properties compared to UFH.[1, 28] Due to a lower extent of binding to certain plasma and cellular proteins, LMWHs have a more predictable anticoagulant response. Therefore, routine dosage adjustments and monitoring of anticoagulation activity are not required in the majority of patients. Low molecular weight heparins have longer plasma half-lives, allowing once or twice daily administration, improved subcutaneous bioavailability, and dose-independent renal clearance.[1, 6, 29] While the absorption of SC UFH is poor and fairly unpredictable, the bioavailability of SC LMWHs is greater than 90%. After a SC LMWH dose, peak anticoagulant effect will occur within 3 to 5 hours. The elimination half-life varies slightly between the various LMWHs and is typically between 3 to 6 hours (see Table 11-1). The primary route of elimination for LMWHs is renal, thus in patients with renal impairment the half-life maybe prolonged.[1, 23, 46]

Indications

The use of LMWHs has been evaluated for several arterial and venous indications, including the treatment of acute coronary syndromes, treatment of VTE in the inpatient and outpatient settings, prevention of VTE in high-risk surgical and medical populations.[1, 6] The FDA-approved indications and recommended dosages vary between the available LMWHs (see Table 11-6). In addition to the FDA labeled indications, LMWHs have been evaluated for many off-label uses such as peri-procedure bridge therapy, prevention and treatment of thrombosis in pregnancy, prevention of VTE in stroke patients, acute spinal cord injury, neurosurgery, multiple trauma, critical illness, etc. LMWHs can also be used as a reasonable alternative to warfarin therapy in circumstances when warfarin therapy fails or is contraindicated, or when a prothrombin time/international normalized ratio (PT/INR) for warfarin, or aPTT for heparin therapy cannot be routinely obtained.[1]

Clinical Pearl

Due to their quick onset of action, LMWH can be initiated and administered via the SC route, obviating the need for an initial IV bolus dose in cases of acute venous thrombosis.

Dosing and Administration

Dosing of the LMWHs will depend on the specific product and also on the indication for use (Table 11-6). Fixed dosages are generally used for prophylactic indications and weight-based dosing regimens are administered in cases of acute thrombotic complications such as for treatment of VTE and ACS.[6, 10, 23] The actual body weight should be used for dosing of LMWHs. Restricting the doses to a certain maximum limit, or "dose capping," is not recommended.[47-50] Pharmacokinetic studies in obese patients support dosing of LMWHs based on the actual body weight and do not show accumulation of LMWH concentrations in these patients when compared to average weight patients.[51, 52]

Clinical Pearl

In patients with acute thrombosis, the practice of dose capping or setting a limit of the maximum amount of LMWH administered independent of patient weight is not recommended. The practice of dose-capping can lead to under-dosing in heavy weight patients and a potential increase in recurrent VTE.

LMWHs are usually administered by SC injection in the abdominal wall area or the upper outer part of the thighs.[53] IV bolus doses (enoxaparin 30 mg IV along with the first SC dose or if > 8 hours after the initial SC dose and going for percutaneous coronary intervention) have also been evaluated in the setting of ACS.[16] After an SC injection, LMWHs result in sustained antithrombotic activity allowing a dosing interval of every 12 or 24 hours depending on the indication and the specific agent (Table 11-6).

When given as larger (once-daily) doses, a significantly higher peak plasma concentration will occur.[51] The dose for enoxaparin is expressed

Table 11-6. CD

Indications and Recommended Doses for LMWHs and Fondaparinux

Indications	Enoxaparin	Dalteparin	Tinzaparin	Fondaparinux
VTE Prophylaxis after Hip-Replacement Surgery	30 mg SC Q12 h initiated 12–24 h after surgery OR 40 mg SC Q24 h initiated 10–12 h prior to surgery.	2500 units SC given 6–8 h after surgery, then 5,000 units SC Q24 h OR 5000 units SC Q 24 h initiated the evening prior to surgery	75 units/kg SC Q24 h initiated the evening prior to surgery or 12–24 h after surgery* OR 4500 units SC Q 24 h initiated 12 h prior to surgery*	2.5 mg SC Q24 h initiated 6–8 h after surgery
VTE Prophylaxis after Hip-Fracture Surgery	30 mg SC Q12 h initiated 12–24 h after surgery*	NA	NA	2.5 mg SC Q24 h initiated 6–8 h after surgery
VTE Prophylaxis after Knee-Replacement Surgery	30 mg SC Q12 h initiated 12–24 h after surgery	2500 units SC given 6–8 h after surgery, then 5,000 units SC Q24*	75 units/kg SC Q24 h initiated the evening prior to surgery or 12–24 h after surgery*	2.5 mg SC Q24 h initiated 6–8 h after surgery
VTE Prophylaxis after Abdominal Surgery	40 mg SC Q24 h initiated 1–2 h prior to surgery	2500 units SC 1–2 h prior to surgery, then 2500 units 12 h after surgery followed by 5000 units SC Q24 h	3500 units SC Q 24 h initiated 1–2 h prior to surgery*	2.5 mg SC Q24 h initiated 6–8 h after surgery
VTE Prophylaxis in Acute Medical Illness	40 mg SC Q24 h	5000 units SC Q 24 h	NA	2.5 mg SC Q24 h*
Treatment of VTE (DVT +/- PE)	1 mg/kg SC Q12 h OR 1.5 mg/kg SC Q24 h	100 units/kg SC Q12 h[b] OR 200 units/kg SC Q24 h[b]	175 units/kg SC Q24 h	5 mg SC Q 24 h if weight < 50 kg 7.5 mg SC Q 24 h if weight 50–100 kg 10 mg SC Q 24 h if weight > 100 kg
Unstable Angina or Non-Q-Wave MI	1 mg/kg SC Q12 h[a]	120 units/kg SC Q12 h[b] (maximum dose 10,000 units)	NA	2.5 mg SC Q 24 h*

*Non-FDA approved for indication.

[a]An additional 30-mg IV bolus with the first SC dose has been studied in clinical trials. NA = date not available.

[b]Dalteparin is now FDA approved for the extended treatment of VTE in cancer patients at a dose of 200 units/kg daily given SC for one month, then 150 units/kg daily SC for 5 months. Dalteparin, at doses of 200 units/kg daily SC OR 100 units/kg twice daily SC, has also been evaluated in the treatment of acute VTE (DVT ± PE).

Clinical Pearl

Intermittent dosing regimens for LMWH or fondaparinux should be written as Q 24 hours instead of Q day, or Q 12 hours instead of BID, in order to avoid overlapping therapy (overdosing) secondary to pre-established institutional dosing times. For example, a first dose of a once-daily regimen may be initially given at 0400, and then repeated at 0900 at the daily-established medication administration time.

in milligrams, while dalteparin and tinzaparin are expressed in units of antifactor Xa activity.[1, 6, 46] Pre-filled syringes are available for enoxaparin (treatment and prophylaxis) and dalteparin (prophylaxis). For treatment doses of enoxaparin, the extent of rounding to the nearest 5-mg, 10-mg, or syringe size (or nearest 1–2000 units for dalteparin and tinzaparin for treatment) is unclear. Considering that this class of agents has a therapeutic range wide enough to not necessitate routine monitoring, rounding to the nearest syringe size (weight > 50 kg) is probably feasible in most situations.

Monitoring

Due to the predictable dose-response of LMWHs, routine monitoring of their anticoagulant effect is not necessary in patients whose condition is stable and uncomplicated.[1, 54] The PT, aPTT, and ACT are inappropriate laboratory markers to monitor the anticoagulant effect, as they are only minimally affected by LMWHs. Prior to initiation of LMWH, a baseline PT/INR, aPTT, CBC with platelet count, and serum creatinine should be obtained and documented. Renal function should be periodically assessed during the course of therapy. As HIT is also a concern with LMWH, albeit at a lower incidence than with UFH, platelet counts should be monitored every few (2 to 3) days during the first 2 weeks of therapy, and then periodically thereafter.[1, 6, 29, 40, 42]

While not routinely recommended, measuring a patient's response to LMWH may be warranted in certain high-risk situations such as patients with morbid obesity (weigh more than 150 kg or body mass index more than 50 kg/m^2), very low body weight (less than 50 kg), significant renal impairment (CrCl less than 30 mL/min), neonates and pediatric patients, and pregnant women.[1, 47, 50, 54] In addition, monitoring can also be considered in patients who receive extended therapy (> 1 month) with LMWHs such as cancer patients. Although controversial, measurement of the chromogenic anti factor-Xa activity has been the most widely used method in clinical practice to measure a patient's response to LMWH and is the method recommended by the College of American Pathologists and the 7th ACCP Conference on Antithrombotic and Thrombolytic Therapy.[1, 54] In the setting of major renal failure, it should be noted that other anticoagulant effects may become more predominant, and separately, the approaches to hemodialysis can influence outcomes independent from the measured anti-Xa activity. Given the limited evidence correlating outcomes with dosing adjustments based on anti-Xa activity, its use as a sole factor for adjusting therapy should be cautioned.

When measuring anti-Xa activity, the sample should be obtained after steady-state concentrations of the LMWH are attained, after the 2nd to 3rd dose. Most available data in the literature support the measurement of peak concentrations, which occur approximately 4 hours after a subcutaneous dose.[47, 55] Trough concentrations can be

Clinical Pearl

Although an absolute correlation between LMWH anti-Xa activity and patient efficacy and safety outcomes have not been clearly established and its use is highly controversial, until better markers for LMWH monitoring will be developed, the anti-factor Xa activity is considered the best biological marker to aid with LMWH dosing and is used in practice in the specific scenarios highlighted above.

Clinical Pearl

Dosing of various LMWHs can be at times confusing as some agents are dosed in milligrams/weight and others as units of antifactor Xa activity/weight. As a practical conversion tool, 1 mg of LMWH-enoxaparin is equivalent to 100 international units antifactor Xa activity.

more useful to rule out drug accumulation, such as in patients with renal failure, and are typically measured just prior to the next dose of the LMWH. While there is some variation in the target concentrations reported in the literature, peak anti-Xa concentrations of 0.1–0.4 units/mL with twice daily dosing are recommended for prevention of VTE, but a more conservative range is 0.2 to 0.4 units/mL. For the treatment of VTE, peak concentrations of 0.4–1.1 units/mL with twice daily dosing have been suggested, but a more conservative therapeutic range is 0.5–1.0 units/mL. With once daily dosing, as higher doses of drug are given per dose, peak concentrations of 1.0–2.0 units/mL have been suggested, but supporting data is even more limited. Although no clear correlation of anti-Xa activity with efficacy and safety outcomes exists, some data suggests that anti-Xa concentrations of greater than 1.0 units/mL in venous indications and greater than 1.5 units/mL in arterial indications have been associated with an increased risk of bleeding.[1, 54-56] Specific algorithms for dosing adjustments based on antifactor Xa activity have not been widely evaluated and are limited at the present time. One dosing approach has been suggested in pediatric patients that can also be potentially applied in adult populations (see Table 11-7).[57]

Clinical Pearl

When monitoring anti-Xa activity, verify that the level was drawn at the pre-selected time post dose (i.e., 4 hours post dose for peak levels), and is consistently done this way for subsequent measurements.

Side Effects, Precautions, and Contraindications

Similar to UFH, bleeding is the most common complication associated with LMWHs.[1, 37] The frequency of major or life threatening bleeding appears to be similar or in some reports lower with LMWHs than with UFH,[58] although this has not been consistently demonstrated in individual clinical trials. In patients at a high acute risk for bleeding, an UFH infusion for ease of adjusting and reversing anticoagulant effects may be desired. Bruising at the injection site is frequently reported with the use of LMWHs. The incidence of bleeding varies with the patient population treated, the indication, dose, and specific LMWH administered.[1, 37, 46]

Spinal and epidural hematomas have been linked to the use of LMWHs in patients undergoing spinal and epidural anesthesia or spinal puncture.[1, 10, 59] Concurrent use of LMWH and all other agents that impact hemostasis in patients with in-dwelling epidural catheters should be strictly avoided as they further enhance the risk of spinal hematoma formation.[10, 59] When inserting and removing the in-dwelling epidural catheters, great care should be used in appropriately coordinating the timing of the dosing of LMWH (see Table 11-8).

Table 11-7. CD

Sample LMWH Dosing Nomogram for Pediatric Patients

AntiXa Level	Hold Next Dose	Dosage Change	Next AntiXa Level
<0.35 units/mL	No	↑ 25%	4 h after next dose
0.35–0.49	No	↑ 10%	4 h after next dose
0.5–1.0	No	No	Next day, then in 1 week, then monthly
1.1–1.5	No	↓ 20%	Before next dose
1.6–2.0	3 h	↓ 30%	Before next dose and 4 h after next dose
>2.0 units/mL	Until antiXa < 0.5 units/mL	↓ 40%	Before next dose and q12h until antiXa <0.5 units/mL

Source: Adapted from: Monagle P, et al. *Chest.* 2001;119 (suppl 1):344–70.

Clinical Pearl

In patients with planned invasive or surgical procedures associated with increased risk of bleeding, the presence of an LMWH should be recognized and the dose held in a sufficient amount of time to allow for drug elimination in order to reduce potential bleeding complications but at the same time minimizing the risk for thrombosis. This step should be repeated post procedure in determining the appropriate time of restarting anticoagulation.

The incidence if HIT is lower with LMWH compared to UFH.[60] However, low molecular weight heparins cross-react with heparin antibodies *in vitro* and should not be given as an alternative anticoagulant in patients with a diagnosis of HIT. Similarly to UFH, platelet counts should be monitored in all patients receiving an LMWH preparation and any signs of thrombocytopenia should be thoroughly evaluated.[1, 40, 42] The risk of osteoporosis appears to be lower with the long-term use of LMWHs when compared to UFH.[1, 46, 61, 62]

Fondaparinux

Pharmacology

Fondaparinux is the first agent in a class of synthetic anticoagulants that selectively inhibit factor Xa activity. Also known as "pentasaccharide," its molecule is composed of the five specific saccharide units that bind to antithrombin (see Figure 11-1).[2, 6] Similar to UFH and LMWH, fondaparinux, by modifying antithrombin activity, is an indirect inhibitor of factor Xa. Through its interaction with antithrombin, fondaparinux inhibits factor-Xa, which in turn mediates the ultimate steps in the coagulation cascade of inhibiting thrombin generation and thrombus formation. The binding of fondaparinux to antithrombin causes a conformational change in the antithrombin's active site which in turn enhances anti-factor Xa activity by approximately 300-fold. The fondaparinux-antithrombin bond is reversible in nature, and the fondaparinux molecule is released to bind several other antithrombin molecules.[2, 7, 63]

In contrast to UFH and LMWH, at therapeutic plasma concentrations, fondaparinux has no direct effect on thrombin (factor IIa) activity. The selective inhibition of factor Xa without a direct effect on thrombin preserves its regulatory functions in the control of hemostasis, which may confer some beneficial characteristics to fondaparinux in wound healing. Unlike UFH or LMWH, fondaparinux does not affect platelet function. As synthetic drugs, factor-Xa inhibitors like fondaparinux cannot transmit animal pathogens, are consistent from batch-to-batch, and can be available in an unlimited supply.[3, 29, 64] This may also be a factor to consider if a non-porcine derived product is requested by a patient for religious concerns.

Clinical Pearl

To date, no cases of HIT have been reported with the use of fondaparinux. Although published data is very limited, the use of SC fondaparinux in cases of sub-acute HIT (platelets are recovered) as a bridge to warfarin therapy can be an attractive alternative to agents like argatroban or lepirudin. The dose in this setting has not been established and may depend on the specific indication for use.

Clinical Pearl

Removal of epidural catheters should be timed and performed at trough LMWH concentrations, i.e., after a minimum of 12 hours has elapsed after the last dose of the LMWH in patients with normal renal function. The next LMWH dose should not be given sooner then 2 hours after removing the catheter (also see Table 11-8).

Pharmacokinetics/Pharmacodynamics

After subcutaneous administration, fondaparinux is completely (100%) absorbed and peak plasma concentrations are reached within 2 to 3 hours.[2, 63] A long elimination half-life of 17 to 21 hours allows once daily administration, however the anticoagulant effect of fondaparinux will persist for 2 to 4 days after stopping the drug. In patients with renal impairment the anticoagulant effect persists even longer.[2, 6, 65]

Table 11-8. CD

Recommendations for Timing of Anticoagulant Agents in Patients Undergoing Neuraxial Procedures

Anticoagulant Agent	Minimum Time Between Anticoagulant Dose and Insertion of Spinal Needle or Placement of Epidural Catheter	Minimum Time Between Insertion of Spinal Needle or Placement of Epidural Catheter and Anticoagulant Dose	Minimum Time Between Anticoagulant Dose and Removal of the Epidural Catheter	Minimum Time Between Removal of the Epidural Catheter and Anticoagulant Dose
Therapeutic dose UFH (IV or SC)	aPTT < 40 seconds and > 4 h post IV infusion or > 12 h post SC dose	Avoid while catheter is in place	Avoid while catheter is in place; aPTT < 40 seconds and > 4 h post IV infusion or > 12 h post SC dose when anticoagulant effect is at minimum	2 h
Prophylactic dose SC UFH (5,000 units q12h or q8h)	No Time Restrictions Apply			
Fondaparinux: therapeutic or prophylactic doses	36 to 48 h*	Avoid while catheter is in place	Ideally avoid while catheter is in place; Just before the next dose and when anticoagulant effect is at minimum	2 h
Therapeutic dose LMWH (enoxaparin 1mg/kg SC q12h or enoxaparin 1.5 mg/kg SC q24h or dalteparin 100 units/kg SC q12h or dalteparin 200 units/kg SC q24h or tinzaparin 175 units/kg SC q24h)	24 h*	Avoid while catheter is in place	Ideally avoid while catheter is in place; Just before the next dose and when anticoagulant effect is at minimum	2 h
Prophylactic dose LMWH (enoxaparin 30mg SC q12h or enoxaparin 40mg SC q24h or dalteparin 5,000 units SC q24h)	10 to 12 h*	Avoid while catheter is in place	Ideally avoid while catheter is in place; Just before the next dose and when anticoagulant effect is at minimum	2 h

* Longer elimination times will be required in patients with impaired renal function. h = hours.
Source: Horlocker 2003.[59]

Clinical Pearl

To minimize bleeding in patients receiving fondaparinux and who are scheduled for surgical intervention, careful timing of the procedure should be considered as the effect of fondaparinux can persist even as long as 2–4 days after the last dose.

Fondaparinux binds specifically to antithrombin and unlike heparin it does not bind to other cellular proteins such as albumin, glycoprotein, platelets, or platelet factor 4.[2, 3, 63] Due to a predictable and linear dose-response relationship, fondaparinux does not require routine coagulation monitoring or dose adjustments. It is distributed in the blood and elimination is mainly renal as unchanged drug. In patients with renal impairment drug accumulation has been reported.[2, 6, 29, 64] Due to an increased risk of bleeding, fondaparinux is contraindicated in patients with severe renal dysfunction (creatinine clearance < 30 mL/min). As fondaparinux is not metabolized in the liver, it has no major pharmacokinetic drug interactions. However, care should be used when fondaparinux is used concurrently with other antithrombotic agents due to an increased risk of bleeding complications.[65]

Indications

Fondaparinux has been evaluated and has demonstrated efficacy in the prevention and treatment of both venous and arterial thrombosis.[66-68] Fondaparinux is FDA-approved for the prevention of VTE following orthopedic (hip fracture, hip replacement, and knee replacement) surgery, prevention of VTE following abdominal surgery, and for the treatment of acute DVT and PE.[65] Fondaparinux has also been evaluated for the prevention of VTE in medical patients and in the treatment of patients with ACS, however these indications are not currently approved by the FDA.[69-71]

Clinical Pearl

Care should be used when fondaparinux is used for an extended time (> 7–10 days) in patients with moderate renal impairment (CrCl 30–50 mL/min), as accumulation of the drug has also been reported in these patients at a rate of approximately 40%.[65]

Dosing and Administration

When used for VTE prevention after abdominal surgery, orthopedic surgery, and in medically ill patients, the dose of fondaparinux is 2.5 mg injected subcutaneously once daily (Table 11-6). In surgical patients, the first dose is typically initiated 6 to 8 hours following surgery. Initiating fondaparinux too soon (i.e., < 6 hours) after surgery should be avoided as there is a direct relationship between the timing of the first dose and the risk of major bleeding complications.[65, 66] In cases where immediate post-operative bleeding is a concern, delaying the initiation of the first dose of fondaparinux until the morning after the orthopedic surgery has also been demonstrated to be effective.[72] For VTE prevention, the usual duration of therapy ranges from 5 to 14 days, depending on the patient population and the specific indication. After hip fracture or hip replacement surgery, fondaparinux can also be given as extended VTE prophylaxis for up to 30 days.[10]

Clinical Pearl

The dose of fondaparinux for obese patients (> 100 kg) with VTE is 10 mg SC every 24 hours, and it is not necessary to adjust upwards to total body weight as is the case for the LMWHs.

Interestingly, in the treatment of patients with ACS, the same dosing regimen of 2.5 mg given subcutaneously once daily has been demonstrated to be effective, similar for its use in VTE prevention.[69, 70] The lower dosing regimen of 2.5 mg once daily was selected for the ACS indications due to a lack of dose-efficacy response of fondaparinux at higher doses in the initial Phase II dose ranging studies.[73] Similarly, no dose response for recurrent thrombosis or bleeding with doses up to 10 mg were observed for use in the initial treatment of DVT or PE. Since the higher doses demonstrated to be effective, the phase III trials for DVT and separately PE used dosing based on the patient's actual body weight.[67, 68] For patients who weigh between 50 kg to 100 kg, the dose of fondaparinux is 7.5 mg given SC once daily. Patients who weigh more than 100 kg should be given 10 mg once daily and those who weigh less than 50 kg should receive only 5

mg daily. Similar to the LMWHs, fondaparinux is administered via the SC route as a once-daily injection. Injection sites include the abdominal wall and the upper, outer parts of the thighs, and the site should be alternated with each injection.[65]

Monitoring

In patients treated with fondaparinux, due to its predictable dose-response, routine monitoring of coagulation parameters is not required.[2, 63] Fondaparinux has no clinically relevant effect on coagulation tests such as the thrombin time, aPTT and PT. In certain high-risk circumstances (suspected over- or under-dosing, renal insufficiency or severe bleeding complications) anti-factor Xa measurement may be considered in order to examine the biologic activity of fondaparinux in comparison to its plasma concentration and for dose guiding. However, caution must be used as the specific parameters for testing and monitoring are not as well defined for this agent as for the heparins, and as mentioned for phase II trials in ACS and VTE, no dose-related response between bleeding and recurrent thrombotic complications were noted up to 10 mg.[6, 50, 74, 75] When measuring the biologic activity of fondaparinux, the use of a chromogenic anti-factor Xa assay and a fondaparinux standard curve should be used. Chromogenic anti-factor Xa assays calibrated with fondaparinux have been shown to reach the equivalence criteria for plasma samples and provide fairly reliable results.[74-76] Prophylactic treatment with 2.5 mg of fondaparinux in orthopedic surgery patients resulted in concentrations between 0.2 and 0.7 mcg/mL at 3 hours after the subcutaneous injection.[77]

Renal function should be documented at baseline and then closely monitored during the course of therapy. If the creatinine clearance drops below 30 mL/min, fondaparinux therapy should be held. Patients receiving treatment with fondaparinux should be closely monitored for signs and symptoms of bleeding complications. Care should be used especially in patients with a creatinine clearance between 30 and 50 mL/min as drug accumulation can occur. As with other anticoagulants, a CBC should be monitored periodically to screen for possible occult bleeding. In patients who received spinal anesthesia, close monitoring for any signs and symptoms of neurological impairment should be performed.[2, 6, 29, 63]

Clinical Pearl

If measurement of anti-factor Xa activity is necessary while a patient is treated with fondaparinux therapy, expect 4-hours peak levels to be higher then those we see typically with the LMWHs as fondaparinux is a pure factor-Xa inhibitor.

Side Effects, Precautions, and Contraindications

Similar to the heparins, bleeding is the major side effect associated with fondaparinux therapy. An inverse correlation between patient weight and major bleeding complications has been reported with the VTE prophylaxis dose (2.5 mg) of fondaparinux.[63, 65, 66] Fondaparinux is contraindicated for VTE prophylaxis in patients who weigh less than 50 kg. The VTE treatment dose is reduced to 5 mg given every 24 hours in patients who weigh less than 50 kg.[65] Due to its long half-life and the risk of spinal hematoma, great caution should be used if fondaparinux is administered in patients receiving neuraxial or spinal anesthesia. Appropriate timing of the fondaparinux dosing and also the timing of the placement and pulling of the epidural catheter is extremely critical (Table 11-8).[59, 78] Thrombocytopenia has been reported to a similar extent as with the LMWHs, however no cases of heparin-induced thrombocytopenia have been reported to date with fondaparinux.[2, 63, 64]

Reversal of Anticoagulant Effect

Unfractionated Heparin

Protamine sulfate is the antidote used to reverse the anticoagulant effect of UFH.[1, 79, 80] To minimize the risk of severe adverse reactions such as hypotension and bradycardia linked to its administration, protamine should be given as a slow IV infusion over 3 to 5 minutes. Once administered, protamine neutralizes the effect of UFH in approximately 5 minutes and its activity will last for approximately 2 hours. One mg of protamine sulfate neutralizes approximately 100 units of UFH. The maximum recommended single dose of protamine is 50 mg, however multiple repeated doses may be necessary if hemorrhage persists. Due to the short half-life of UFH ($\sim$60 min) when given as an IV infusion, only the dose given over the last 3–4 hours needs to be included in the protamine dose calculation. When given via the SC route, a longer protamine infusion time or repeated administration may be necessary. The patient's coagulation status should be closely monitored using the aPTT test in order to assess response to protamine therapy.[1, 80, 81]

LMWH

While there is no complete antidote for LMWHs, protamine can be used as a partial reversal agent for the effects of LMWH.[1, 79] Although protamine neutralizes the antithrombin activity of LMWH, it only neutralizes approximately 60% of their anti-factor Xa activity.[1, 82, 83] If LMWH was given in the previous 8 hours, then 1 mg of protamine should be administered for every 100 units (or 1 mg) of the LMWH. If the LMWH dose was given in the previous 8 to 12 hours, a 0.5-mg dose of protamine should be given for every 100 anti-factor Xa units. The use of protamine sulfate is not recommended if the LMWH was administered more than 12 hours earlier.[1, 79, 81]

Fondaparinux

Fondaparinux is not reversed by protamine, and at this time no specific antidote is available to reverse its antithrombotic activity.[79] In the event of major bleeding, fresh frozen plasma and factor concentrates should be given. In the case of a life-threatening bleed, recombinant factor VIIa has been shown to reverse effects in vitro for 2–4 hours, but is a very costly option and can also promote thrombosis formation.[84, 85]

Clinical Pearl

Patients with fish allergies are at risk for developing anti-protamine antibodies and allergic reactions to protamine. These patients can be pretreated with steroids and antihistamines.

Special Patient Populations

In selected high-risk populations, such as patients at high risk of bleeding, need for emergent invasive procedures, and presence of renal insufficiency, UFH often is the preferred anticoagulant agent because of its relatively short half-life and its potential for rapid reversal. Acute traumatic injury or extra-corporeal membranous oxygenation (ECMO) are frequently associated with reduced levels of AT and an increased risk for thromboembolic complications. In such situations, a heparin infusion may be desired over other anticoagulants due to the ease of frequently measuring and evaluating the anticoagulant effect.

Clinical Pearl

In patients with anasarca, reduced bioavailability of SC injections may preclude the potential for achieving adequate anticoagulation for either UFH or LMWH. In such situations, UFH infusion targeting a low-intensity increase in the aPTT may be used for VTE prophylaxis.

Renal Impairment

The elimination of UFH is dose-dependent and due to its ability to be monitored and dose adjusted, its use in patients with renal impairment has not been historically considered a major clinical challenge. Irrespective of the anticoagulant used, a higher incidence of major bleeding exists as renal function declines. Thus, UFH may be the preferred agent for patients with notable renal dysfunction, or those requiring hemodialysis.[1, 86] In the setting of intermittent hemodialysis, minimal amounts of systemic heparin may be used, and the dialyzer may be pre-bathed in heparin. In extended duration therapies, and more so in continuous renal replacement therapies, a greater intensity of anticoagulation (typically using heparin) is necessary. Rates can depend on the type on hemodialysis involved. In contrast, the LMWHs and fondaparinux are primarily cleared via renal excretion and pharmacokinetic data suggests that as renal function decreases, the half-life of LMWHs and fondaparinux increases, and their clearance decreases.[87, 88] Reduced elimination can result in increased drug concentrations and an increased bleeding risk. The actual degree of accumulation is different for the various LMWHs and fondaparinux, as there are differences in their pharmacologic profiles (Table 11-9).

Because the large clinical trials have generally excluded patients with renal impairment, efficacy and safety outcomes in these patients are not well-documented, and clear dosing and monitoring guidelines are lacking for most of the agents.[47, 88] Dosing estimates can be however inferred from our understanding of kinetic studies with the various agents. The 7th ACCP panel and many other experts still recommend the use of UFH to provide full therapeutic anticoagulation in patients with severe renal impairment (CrCl less than 30 mL/min).[1, 88] If LMWH is used, then monitoring of anti-Xa activity should be considered in patients with a CrCl less than 30 mL/min, or in patients with mod-

Table 11-9. CD

Dosing and Monitoring Considerations for LMWH and Fondaparinux in Patients with Renal Impairment

Anticoagulant	Pharmacokinetic Considerations	Dosing and Monitoring Recommendations	Package Insert Recommendations
Dalteparin	CrCl < 30* mL/min: no accumulation noted up to 1 week of therapy CrCl 30 to 50 mL/min: no accumulation noted	CrCl < 30* mL/min: no dose adjustment needed up to 1 week For use > 1 week, consider monitoring of anti-Xa activity and adjust dose if accumulation is noted CrCl 30 to 50 mL/min: no dose adjustment needed	CrCl < 30* mL/min: use with caution
Enoxaparin	CrCl < 30* mL/min: 40% to 50% accumulation noted CrCl 30 to 50 mL/min: 15 to 20% accumulation noted	CrCl < 30* mL/min: Consider a 40% to 50% dose decrease and subsequent monitoring of anti-Xa activity CrCl 30 to 50 mL/min: Consider a 15% to 20% dose decrease with prolonged use (> 10–14 days) and subsequent monitoring of anti-Xa activity	CrCl < 30* mL/min: Prophylaxis–30mg SC daily Treatment–1mg/kg SC daily
Tinzaparin	CrCl < 30* mL/min: 20% accumulation noted CrCl 30 to 50 mL/min: no accumulation noted	CrCl < 30* mL/min: consider a dose decrease of 20% and subsequent monitoring of anti-Xa activity CrCl 30 to 50 mL/min: no dose adjustment needed	CrCl < 30* mL/min: use with caution
Fondaparinux	CrCl < 30* mL/min: 55% accumulation noted CrCl 30 to 50 mL/min: 40% accumulation noted	CrCl < 30 mL/min: only use if able to measure anti-Xa activity to guide with dose adjustment CrCl 30 to 50 mL/min: if prolonged use (> 10–14 days) consider measurement of anti-Xa activity to guide with dose adjustment	CrCl < 30 mL/min: contraindicated CrCl 30 to 50 mL/min: use with caution

* Data is very limited in patients with a CrCl < 20 mL/min; in patients on hemodialysis, limited data is only available for thrombosis prevention in the dialysis circuit but NOT for the prevention and/or treatment of venous or arterial thrombosis. Thus, until further data is available UFH is the agent of choice in patients on hemodialysis or with a CrCl < 20 mL/min.

erate renal impairment with a CrCl 30–50 mL/min and if the LMWHs are used for extended periods of time (greater than 10–14 days).[1, 55, 56] Fondaparinux is contraindicated in patients with CrCl < 30 mL/min, and care should be used when administered in patients with CrCl of 30 to 50 mL/min as drug accumulation can occur, especially with prolonged used (see Table 11-9).[29, 65] Elderly patients are also more likely to have decreased renal function and careful assessment of renal status should be conducted prior to initiating therapy with any of these agents.

Extremes of Body Weight

Total body weight appears to be a good predictor for dosing of LMWHs in obese patients. Setting a maximum dose (or dose capping) is not recommended, and in fact it may result in under-dosing of these patients with a potential increase in thrombotic complications.[48, 55, 56] Monitoring of anti-Xa activity is generally not recommended; however, as only a very limited number of patients with total body weight greater than 150 kg have been included in the large LMWH treatment clinical tri-

als, it may be reasonable to consider anti-factor Xa measurement in these patients for the purposes of dose guiding.[1, 54, 56] For prophylaxis indications, available data suggest that fixed LMWH doses may not be sufficient in morbidly obese patients.[55, 56] In the absence of clear dosing guidelines of LMWHs for prophylaxis in obese patients, a 25%–30% dose increase or weight based dosing of 50 units/kg/day may be considered.[1, 47, 56]

In contrast, low weight patients (i.e., < 50 kg) may be at risk for drug accumulation and bleeding complications when fixed prophylactic doses of LMWH or fondaparinux are administered. Due to a concern of increased bleeding complications, when used for VTE prophylaxis in surgical patients, fondaparinux is contraindicated in patients who weigh less than 50 kg. When used for VTE treatment, the dose of fondaparinux is lowered to 5 mg daily in patients who weigh less than 50 kg.[1, 56, 65]

Pregnancy

The heparins, UFH or LMWH, are the anticoagulants of choice during pregnancy.[62] UFH is FDA pregnancy category C, and as it does not cross the placenta it has not been associated with teratogenicity.[89] During the last trimester and in the peripartum period, UFH should be used with caution in order to minimize the risk of potential maternal hemorrhage. UFH is not excreted in breast milk and can be used safely by women who are breastfeeding. The LMWHs (dalteparin, enoxaparin, and tinzaparin) are classified as FDA pregnancy category B, they do not cross the placenta, and are not excreted in breast milk.[61, 62] The LMWHs appear to be relatively safe to use during pregnancy and are an attractive alternative to UFH when long-term anticoagulation therapy is required. In contrast to UFH, the LMWHs do not appear to affect bone formation with long-term administration. Because the pharmacokinetics of low-molecular-weight heparins may change during pregnancy, monitoring anti-Xa activity every 3 to 4 weeks for dose guiding should be considered.[61, 62] Induction of labor is advisable so that UFH and LMWH can be discontinued prior to delivery to minimize the risk for excessive bleeding during delivery.[62]

Fondaparinux is categorized as FDA pregnancy category B as it does not appear to cross the placental barrier.[65, 90] There is limited information regarding the use of fondaparinux during pregnancy.[91] Fondaparinux is excreted in the milk of lactating rats, but excretion in human milk is unknown. Until more data becomes available, UFH and LMWH should remain the agents of choice in pregnant patients.[65]

Clinical Pearl

Women who develop HIT during pregnancy or have a recent history of HIT (e.g., less than 3 months) cannot use UFH or LMWH safely. Potential treatment alternatives with a DTI should be considered. Lepirudin is known to cross the placenta, however case reports suggest it may be safe for the management of HIT with thrombosis in pregnancy. Limited case reports suggest that fondaparinux may also be a future potential alternative in pregnant patients, however, a dose has not been established.

Pediatric Patients

UFH and LMWH are commonly used anticoagulants in children requiring antithrombotic therapy. The most common form of thrombosis in children is usually seen in the upper extremity where vascular access lines have been placed. For the treatment of acute thrombosis, the dosage of UFH will vary with age. An initial loading dose of 75 to 100 units/kg over 10 minutes followed by a maintenance dose of 28 units/kg/hour for infants up to 12 months and 20 units/kg/hour for children 1 year old or greater has been suggested.[92,93] Unfortunately, heparin adjustment protocols and algorithms are not readily available in the pediatric population. Some algorithms have proposed adjustments based on a percentage of the dose. In patients requiring very small amounts of UFH, the required changes in infusion rate may be very small, thus requiring a considerable amount of time to achieve desired target values. In contrast, high infusion rates may lead to overshooting the target values secondary to more notable changes required in the infusion rate. It should also be noted that most of the laboratory target values are based on data from adults, and have not been necessarily validated in the pediatric population.[92]

Due to their convenience of use, the LMWHs are becoming the preferred agents in pediatric populations despite limited data to test their safety and effectiveness in this setting. Weight-based LMWH doses provide a less predictable anticoagulant response in children compared to adults, thus periodic monitoring of anti-Xa activity for dose guiding should be considered (Table 11-7).[92, 94] Neonates or infants are at increased risk for having antithrombin deficiency. Various anti-Xa activity assays are currently available that may or may not include a

step to spike the sample with antithrombin prior to measuring. If such a step is present, the presence of subtherapeutic anticoagulation may be missed. Because of the challenges in monitoring UFH or using warfarin in pediatric patients, the use of LMWHs has been explored. Although the incidence of HIT in pediatric patients is most likely lower then in adults, HIT has also been reported in these patients and it should be considered when monitoring therapy.[95]

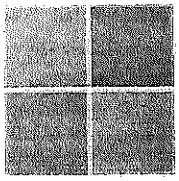
For enoxaparin, suggested therapeutic doses are 1.5 mg/kg every 12 hours for infants younger then 2 months and 1.0 mg/kg every 12 hours for those older then 2 months. The suggested dose for dalteparin is 86 to 172 units/kg every 24 hours keeping in mind that neonates appear to require higher doses/kg than older children or adults.[92,94,96] Fondaparinux use in pediatric populations has not been studied. When used in smaller doses, enoxaparin may have to be diluted to accurately allow for measurement of the dose. This dilution has been shown to maintain appropriate anti-Xa activity for up to 2 weeks.[97]

Conclusion

A complexity of factors can affect the appropriate and safe use of UFH, LMWH and fondaparinux in daily clinical practice. Clinicians involved in managing and monitoring various antithrombotic therapies need to carefully consider all the clinical nuances in selecting, dosing, and monitoring UFH, LMWH, and fondaparinux to allow for their effective use and minimize related complications.

Clinical Pearl

Monitoring of anti-Xa activity for LMWH has been suggested in multiple populations where unique dosing approaches may be present. Unfortunately, specifics and outcomes with this approach are limited at best. When using an anti-Xa activity level, consider how you will respond when the value is reported. Use caution if consistently low values lead to notably high dosing regimens and potentially increasing the risk for bleeding. In contrast, consistently high values may drive the dosing regimen down and increase risk for thromboembolism.



Patient Case

KE is a 29-year-old female who presents to the ER with complaints of LLE pain, erythema, and swelling. Her symptoms started 4 days ago and have gotten progressively worse. Of note is that she is 3 months pregnant, with no previous pregnancies reported. An ultrasound was ordered and she was diagnosed with a DVT involving her L iliac and femoral veins. She is admitted for treatment.

Past Medical History:
Pregnancy loss x 2
Family History:
Mother died of a PE
Maternal grandmother died of a stroke
Social History:
Non significant
Current Medications:
Pre-natal vitamin 1 tablet by mouth daily
Folic acid 1 mg daily
Allergies:
No known drug allergies
Physical Examination:
Vital signs: blood pressure = 125/65, heart rate = 92, respiratory rate = 20, temperature = 38 °C
Weight: 69 kg; height: 65 inches
Labs:
Within normal limits
Estimate GFR = 101 mL/min
Tests:
Doppler US: (+) for ileo-femoral DVT

1. **What are appropriate acute-phase treatment options in this patient?**

   Anticoagulation therapy needs to be initiated promptly in order to minimize clot extension and PE. For the initial acute phase therapy, full therapeutic doses of IV UFH or SC LMWH are both appropriate treatment options. As the patient is hospitalized, UFH is selected as initial therapy.

2. **Discuss dosing and monitoring of UFH in this patient.**

   A weight-based UFH dosing regimen should be considered, as these regimens are more likely to reach the therapeutic aPTT threshold in the first 24 hours after initiating treatment as compared to more traditional dosing regimens. UFH can be safely used in pregnancy. An IV bolus dose of UFH of 80 units/kg (5,500 units) should be given, followed by an infusion at a rate of 18

units/kg/hour (1,200 units/hour). The patient's actual body weight should be used for dose calculation. Loading doses are usually rounded to the nearest 500 units and infusion rates are rounded to the nearest 100 units for ease of administration. The aPTT should be obtained at baseline, and then at 6 hours after initiating the UFH infusion. Subsequent aPTTs should be obtained at 6 hours after each dose change. Once the patient is stabilized and the aPTT is within therapeutic range, monitoring can be extended to every 24 hours as long as the patient is on therapy. The goal aPTT will be institution specific, to correspond to a plasma heparin concentration by anti-factor Xa activity of 0.3–0.7 units/mL. At this institution, the target aPTT range has been determined by the laboratory to be 60 to 90 seconds.

3. The first aPTT, drawn 6 hours after initiating the UFH infusion, comes back at 102 seconds. The UFH infusion rate needs to be decreased according to the nomogram highlighted in Table 11-5 (or a similar institution based nomogram). A dose decrease by 1 unit/kg/hour (~70 units/hour down from 1,200 units/hour to 1,100 units/hour) is suggested in this patient. The aPTT should be checked again at 6 hours after the new infusion rate has been initiated, and further dosing adjustments should be made as necessary.

4. **After additional dose adjustments, the patient's UFH infusion has been maintained at 1,000 units/hour. After completing 5 days of IV UFH therapy, the decision was made to send the patient home. Discuss anticoagulant agent selection, dosing, and monitoring considerations.**

   As this patient is not a candidate for warfarin, due to its teratogenic potential in pregnancy, she will need to be treated with a SC anticoagulant (SC adjusted dose UFH or SC therapeutic LMWH) for the remainder of her pregnancy. Adjusted-dose SC UFH is selected as she cannot afford to pay the cost of an LMWH, due to lack of insurance coverage for medications. The patient's 24-hour UFH dose requirement is calculated at 24,000 units. This dose is then increased (usually by 10%–20%) to account for the more limited bioavailability of the SC route of administration. In our patient, a reasonable dose adjustment would be to increase the dose to 27,000 units or approximately a 12.5% increase in dose. This dose is then divided in two, and the patient's initial SC UFH will be 13,500 units SC given every 12 hours. The IV UFH infusion is discontinued and within 1 hour of stopping the infusion, the first SC UFH dose should be administered to ensure that the peak anticoagulant levels are reached in a timely fashion. The aPTT should be checked at 6 hours after the SC dose and monitored frequently until the patient's dose is stabilized. Once the dose is stabilized, monitoring of aPTT should be performed at least weekly throughout her pregnancy as dose requirements may change due to progressive weight gain and changes in glomerular filtration rate.

References

1. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126(3 Suppl):188S-203S.
2. Weitz JI, Hirsh J, Samama MM. New anticoagulant drugs: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126(3 Suppl):265S-286S.
3. Hoppensteadt D, Walenga JM, Fareed J, Bick RL. Heparin, low-molecular-weight heparins, and heparin pentasaccharide: basic and clinical differentiation. *Hematol Oncol Clin North Am.* 2003;17(1):313-41.
4. Heparin Sodium Prescribing Information. Accessed January 2007.
5. Hirsh J, Anand SS, Halperin JL, Fuster V. Guide to anticoagulant therapy: heparin. *Circulation.* 2001;103:2994-3018.
6. Nutescu EA, Shapiro NL, Chevalier A, Amin AN. A pharmacologic overview of current and emerging anticoagulants. *Cleve Clin J Med.* 2005;72 Suppl 1: S2-6.
7. Alban S. From heparins to factor Xa inhibitors and beyond. *Eur J Clin Invest.* 2005;35(Suppl 1):12-20.
8. Bussey H. Traditional anticoagulant therapy: why abandon half a century of success? *Am J Health-Syst Pharm.* 2002;59(20 Suppl 6):S3-6.
9. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin. *Chest.* 2004;126:188S-203S.
10. Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126(3 Suppl):338S-400S.
11. Raschke RA, Reilly BM, Guidry JR, et al. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. *Ann Intern Med.* 1993;119:874-881.
12. Reilly BM, Raschke RA. New method to predict patients' intravenous heparin dose requirements. *J Gen Intern Med.* 1996;11(3):168-173.
13. Raschke RA, Gollihare B, Peirce JC. The effectiveness of implementing the weight-based heparin nomogram as a practice guideline. *Arch Intern Med.* 1996;156(15):1645-9.
14. Rosborough TK, Shepherd MF. Achieving target antifactor Xa activity with a heparin protocol based on sex, age, height, and weight. *Pharmacotherapy.*