Unfractionated Heparin and Other Antithrombin Mediated Anticoagulants

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ABBREVIATIONS: LMWH = low-molecular-weight heparins; PTT = partial thromboplastin time; TFPI = tissue factor pathway inhibitor; UFH = unfractionated heparin.

INDEX TERMS: coagulation; heparin.

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Several anticoagulants work by enhancing the role of antithrombin (previously called antithrombin III). The group includes one of the oldest anticoagulants, unfractionated heparin (UFH), along with the more recent low-molecular-weight heparins (LMWH), heparinoids, i.e., Danaparoid® that has been removed from the market, and the synthetic drugs fondaparinux and idraparinux, currently in clinical trials. All of these agents work indirectly to inhibit the generation of thrombin and fibrin. They work by binding to antithrombin, creating a marked increase in the affinity of antithrombin for the serine protease active site of the coagulation factor(s) to inhibit their activity. While these drugs share this mechanism of action, the drugs differ in the coagulation factors most targeted for inactivation. Moreover, they differ in their pharmacologic properties leading to significant differences with regard to predictability and flexibility of dosing and administration, as well as toxicity profiles (Table 1).

UNFRACTIONATED HEPARIN

UFH has a long history of clinical benefit for both arterial and venous thrombotic diseases. Despite the advent of newer agents, it still plays an important role in the care of diverse groups of patients and disorders. The familiarity and reversibility of UFH give it some clear advantages. None-

Table 1. Comparison of clinical antithrombin activating agents by type

Agent	Route of administration	Dosing	Target factors	Monitoring	Protamine inhibition
UFH	IV or SC	IV* – continuous infusion SC* – q8-12hrs	IIa = Xa	PTT*	~100%
LMWH*	SC	q12 or q24hrs	Xa >> IIa	Anti-Xa level†	30% to 60%
Synthetic pentasaccharide (fondaparinux)	SC	q24hrs	Xa	Anti-Xa level†	none

* IV = intravenous; SC = subcutaneous; PTT = activated partial thromboplastin time
* Differences exist between the various LMWH; averages and/or ranges given
† Monitoring generally not required

theless, it also presents some definite shortcomings, especially with regard to monitoring needs and potential for severe complications.

UFH consists of heterogeneous-length polysaccharides with sugar subunits having variable sulfation. Molecular weights of individual molecules vary between 3,000 and 30,000 daltons.[1,2] Only about one-third of the administered UFH will have the required specific pentamer sequence that has high affinity for antithrombin and provides the anticoagulant activity. Upon binding to this sequence, antithrombin takes on a new conformation with approximately a 1000-fold increase in its ability to inhibit the serine protease active site of coagulation factors. Thrombin (factor IIa) and factor Xa have the greatest sensitivity to the heparin-antithrombin complex. However, inhibition of thrombin requires polysaccharide molecules of at least 18 units while heparin molecules that contain no more than the specific pentamer sequence can only inhibit factor Xa. Most preparations of UFH give about equal inhibition of these two factors (IIa and Xa).

UFH requires either intravenous or subcutaneous administration. The latter has an associated one to two hour delay in its anticoagulant effect. The rate of clearance for heparin varies inversely according to the molecular length. Thus, the relative levels of factor Xa and thrombin inhibition vary over time. Additional factors that confound predictability of dose effect include heparin binding to plasma proteins and cells such as macrophages and endothelial cells. These cells will also depolymerize the heparin, which is a saturable phase of its clearance. The renal phase is slower and not saturable. This combination of variable protein binding and clearances creates a nonlinear relationship between the antithrombotic effect and heparin dose in the therapeutic range.[3]

Although dose and effect lack a linear relationship, the heparin dose does have a relationship to both efficacy and safety. Thus, monitoring plays a critical role in UFH therapy. Older studies have used a simple activated partial thromboplastin time (PTT) with therapeutic range generally being defined as a ratio of 1.5 to 2.5, patient to control. However, this approach has limitations as it emphasizes the antithrombin activity since factor Xa inhibition has little effect on this assay. In addition, the heparin sensitivity of different available PTT reagents varies.[4] Thus, the best approach standardizes the PTT using either heparin concentration or factor Xa inhibition level.[1] The heparin concentration method sets the therapeutic PTT range to correspond to heparin levels between 0.2 to 0.4 U/mL as determined by protamine titration, and the Xa inhibition method uses a range that corresponds to an anti-Xa level of 0.3 to 0.7 U/mL. Initial monitoring should begin about six hours after the initial bolus dose.

UFH has found use in a wide variety of clinical situations that involve both venous and arterial thromboses. Elucidation of the broad applications for UFH goes beyond the scope of this short review, but may be found in other recent reviews.[2,5] In addition to the familiarity and proven efficacy, UFH enjoys the advantage of being completely reversible. Protamine sulfate can reverse the heparin effect with 1 mg protamine neutralizing about 90 mg of heparin.

Despite the great success of unfractionated heparin, it has significant limitations. First, a high propensity for protein and cell surface binding limits and causes variability in anticoagulant effect with a resulting need for frequent monitoring. Second, the size of the heparin-antithrombin complex prevents it from inhibiting either the factor Xa in the prothrombinase complex or the thrombin attached to fibrin. Third, long term heparin therapy causes osteopenia.[2] Fourth, heparin induced thrombocytopenia (HIT) can occur due to the development of antibodies directed against a complex of heparin and platelet factor 4 (PF4).[6] These antibodies have the ability to activate platelets and cause both venous and arterial thromboses that have been associated with a significant mortality rate.

LOW MOLECULAR WEIGHT HEPARIN

Several LMWHs have entered the market in the U.S. and elsewhere. The primary advantage involves their more favorable pharmacokinetic profile that addresses some of the shortcomings of unfractionated heparin noted above. All LMWHs derive from commercial grade unfractionated heparin that has undergone depolymerization by either chemical or enzymatic digestion. As a result, the LMWHs have an average polymer length of one third that of unfractionated heparin (5,000 daltons for LMWH).[2,7] The size difference accounts for their advantages compared to unfractionated heparin. Because each LMWH has undergone unique processing and little exists in the way of head-to-head comparisons in clinical studies, the ability to interchange them remains unknown.

The smaller molecular weight of LMWHs changes their anticoagulant profile compared to UFH, although both work by enhancing antithrombin activity. Since the LMWH preparations contain far fewer of the large polymers needed for thrombin inactivation, their predominant anticoagulant effect oc-

curs by inhibiting factor Xa. As a result, these agents have little effect on the PTT. However, the clinical, antithrombotic effect seems to involve more than the factor Xa inhibition, and may in part rely on the ability of LMWH to increase the release of tissue factor pathway inhibitor (TFPI).

LMWHs are administered subcutaneously based on body weight and generally reach a peak plasma level around four hours after administration. Their relatively small size gives the average molecule less positive charge and reduced protein binding compared to UFH. Therefore, the LMWHs have a more predictable dose response and longer half-life than UFH. This predictability permits dosing clinically stable adults without the need for monitoring. The kidney serves as the principal route of clearance, but the liver can play a role in depolymerization and desulfation. Thus, patients with liver and/or renal insufficiency may require monitoring during therapy. Other patients for whom monitoring may improve outcomes include those at the extremes of body weight (<40 kg or >150 kg), children, and pregnant women.

The preferred method to monitor LMWH uses a chromogenic anti-Xa assay, although amidolytic assays have also been used. The peak level, as opposed to trough, may provide the most useful information with regard to safety and efficacy.[2] For prophylaxis of venous thromboembolism and treatment of venous thromboembolism the desired anti-Xa levels should fall between 0.1 to 0.2 U/mL, and 0.4 to 1.1 U/mL, respectively. Each assay should be specific for the particular LMWH method and device. Different methods of chromogenic assays and devices have yielded different anti-Xa levels for patients treated with a single type of LMWH.[8] Because differences exist between LMWHs, tests must also be specific to a given type.

Multiple clinical studies have demonstrated the efficacy of the different LMWHs in comparison to UFH. However, the extent and variety of medical situations under which a given LMWH has undergone testing vary considerably. Given the known pharmacologic differences between the multiple LMWHs and the lack of good studies that compare them, it remains unknown if or how one drug might substitute for another.[9] Virtually all LMWH studies have been against UFH. Enoxaparin has undergone the greatest testing and has the most U.S. FDA approved indications (Table 2). As a general rule, the studies to date demonstrate LMWH has equal or more favorable efficacy and toxicity profiles compared to UFH. For some, LMWH defines the new standard of care in certain clinical situations.[10] The LMWHs have also permitted a means to do outpatient treatment for conditions that previously required hospitalization during the use of UFH.[11,12]

Compared to UFH, the LMWHs have two other major advantages. First, they appear to have less associated osteoporosis. This reduced toxicity likely results from their relative decrease in size and, thus, protein and cellular binding leading to reduced osteoclast activation. Second, the LMWHs have a significantly reduced rate of HIT compared to UFH.[13] Nonetheless, HIT can still occur, and the LMWHs cannot replace UFH once HIT develops since significant cross reactivity exists.

Table 2. U.S. FDA approved indications for LMWH

Indication	Enoxaparin	Dalteparin	Tinazeparin	Ardeparin
VTE* prophylaxis after knee arthroplasty	+			+
VTE prophylaxis after hip arthroplasty	+	+		
Extended VTE prophylaxis after hip arthroplasty	+			
VTE prophylaxis after abdominal surgery	+	+		
Inpatient treatment of VTE	+		+	
Outpatient treatment of DVT	+			
Treatment of acute coronary syndrome	+	+		

* VTE = venous thromboembolic disease

The anticoagulant effect of LMWHs does not reverse with protamine to the same extent as UFH.[2] Although differences exist between the various LMWHs, on average only a 40% to 50% neutralization of the anti-Xa activity occurs. Thus, UFH may represent a better option in clinical circumstances that might require the ability to quickly reverse the anticoagulant effect.

SYNTHETIC OLIGOSACCHARIDES

One synthetic pentasaccharide analog, fondaparinux, has received FDA approval for clinical use and another, idraparinux, has entered several phase III clinical trials. Both contain the minimum sequence for high affinity binding to antithrombin. Due to their synthetic nature and therefore purity, these drugs contain only anti-Xa anticoagulant activity. No long polysaccaride chains exist to bridge antithrombin to thrombin. Thus they prevent thrombin generation but possess no antithrombin activity. In contrast to the heparins in which only one-third of the drug has anticoagulant activity, all synthetic pentasaccharide molecules contain the high affinity sequence giving each anticoagulant activity. These drugs also have minimal binding to proteins other than antithrombin.

Both fondaparinux and idraparinux have subcutaneous routes of administration with near complete bioavailability.[14] The standard fixed fondaparinux dose of 2.5 mg reaches a peak concentration approximately three hours after administration and may be given once daily due to a half-life of 15 hours. Clearance occurs through the kidney. Patients with renal impairment have significantly slower clearance. Individuals weighing less than 50-kg and elderly, those greater than age 70, also have reduced clearance. Fondaparinux generally does not require monitoring. If desired, the anti-Xa activity may be used if the comparator is fondaparinux and the level expressed in milligrams of the fondaparinux calibrator.

Idraparinux is a more sulfated version of fondaparinux and has both a greater affinity for antithrombin and a longer half-life, approximately 130 hours, than fondaparinux.[14] The half-life is similar to antithrombin itself, and long enough to permit the current studies to utilize the drug as a weekly injection. At this time, idraparinux has not received FDA approval for clinical use, but is in ongoing clinical phase III studies.

Fondaparinux has received U.S. FDA approval for prevention of DVT in hip replacement, knee replacement, and hip fracture surgeries. The clinical trials demonstrate a greater efficacy in prevention of all venous thromboembolic complications compared with enoxaparin.[15-17] Some of the greater efficacy may reflect the difference in dosing schedules between the two agents. In addition, in knee replacement surgery, major bleeding had a statistically significant increase with fondaparinux.[17]

Neither fondaparinux nor idraparinux bind PF4, and to date no report of a HIT-like complication exists with these agents. Nonetheless, one major drawback for these synthetic medications concerns the lack of any available neutralizing agents. Protamine sulfate does not inhibit the anticoagulant effect for either drug.[14] Thus, patients at significant risk of bleeding with anticoagulation may not be suitable candidates for treatment with fondaparinux at this time.

SUMMARY

Clinical practice over the past decade has evolved to include new agents, LMWH and synthetic polysaccharides, that bind to and enhance the activity of antithrombin similar to UFH. These drugs differ from UFH since their anticoagulant effect consists predominantly, or entirely, of anti-Xa activity. More important, the new drugs have greater predictability with regard to dosing. In clinical studies the new agents have proven as good as or better than UFH with regard to efficacy and toxicity. The synthetic polysaccharide may possess the greatest efficacy, but possibly with increased bleeding risk. However, UFH still has one advantage over these agents, the ability of its anticoagulant effect to undergo essentially complete reversal with an available drug, protamine sulfate. Thus, clinical situations favoring UFH over these newer parenteral agents still exist.

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