Heparin Overview and Issues

Henry Bussey, Pharm.D., FCCP, FAHA, John L. Francis, Ph.D., and the Heparin Consensus Group

Unfractionated heparin (UFH), which has been available commercially for over half a century, has been the most widely used agent for quickly suppressing thrombosis. When given intravenously, UFH quickly binds to and activates antithrombin, which then inhibits several activated factors in the clotting cascade. For decades, UFH was invaluable for treating arterial and venous thrombosis, and no alternative was available. The short half-life of UFH and the fact that its action could be reversed readily with protamine made it an almost ideal antithrombotic agent. However, variable pharmacokinetics, together with problems of inaccuracy and unreliability of the activated partial thromboplastin time, have made it difficult to use this drug optimally. In addition, side effects such as osteoporosis, heparin-induced thrombocytopenia (HIT), and delayed HIT have led to increased concerns about the use of UFH in view of the advantages offered by newer agents. Fractionating heparin into low-molecular-weight heparins that still retain the pentasaccharide active site provided a way to achieve the same type of therapeutic effect with more predictable dosing and fewer adverse effects. Similarly, a pentasaccharide has been synthesized and marketed as fondaparinux. Although these advances have improved our therapeutic options, continued advances on the horizon raise the question of whether the use of UFH will soon be abandoned.

Key Words: unfractionated heparin, activated partial thromboplastin time, pharmacologic limitations, pharmacokinetic limitations, drug-related problems, heparin-induced thrombocytopenia.

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Heparin, referred to as cephalin at the time, was first described in 1916 and became commercially available in the 1940s. This agent, which provided the first truly effective therapy for thromboembolism, has remained a cornerstone of therapy for millions of patients each year for more than half a century. Its ability to inactivate the clotting process quickly has been invaluable in treating patients with various forms of venous or arterial thrombosis. In addition, it has been a leading therapeutic option in preventing thrombosis in a variety of conditions known to increase the risk of thromboembolism. However, many issues continue to challenge the contemporary utility of UFH, such as a complex pharmacokinetic profile, complicated administration process, drug-related problems, and inability to standardize the activated partial thromboplastin time (aPTT). Also, newer anticoagulation agents are available that possess, overall, more favorable profiles.

From the University of Texas Health Science Center, San Antonio, Texas (Dr. Bussey), and the Florida Hospital Center for Hemostasis and Thrombosis, Orlando, Florida (Dr. Francis).

Address reprint requests to Henry Bussey, Pharm.D., FCCP, FAHA, University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78229; e-mail: bussey@uthscsa.edu.

Mechanism of Action

Unfractionated heparin exists as a heterogeneous mixture of polysaccharide chains of different lengths. Molecular weights of these chains range from 3000–30,000 daltons, with a mean of 15,000 daltons or approximately 45 saccharide units. Only about one third of the heparin molecules exert a therapeutic effect at levels

achieved with usual dosages. The ability of heparin to turn off the clotting cascade resides in the pentasaccharide unit of the molecule that binds to the lysine site on antithrombin (previously known as antithrombin III). This produces a conformational change at the arginine-reactive site of antithrombin that accelerates its binding to and subsequent inactivation of the serine center site of specific coagulation factors.

Without UFH, antithrombin is a slow inhibitor (Figure 1).[1] Of the numerous coagulation factors inactivated by the heparin-antithrombin complex, thrombin (factor IIa) and factor Xa are the most responsive and most critical within the clotting cascade. Inhibition of thrombin requires heparin chain lengths consisting of at least 18 saccharide units since a ternary complex must be formed simultaneously between heparin, antithrombin, and thrombin. Factor Xa inhibition requires only the binding of the heparin pentasaccharide sequence to antithrombin (Figure 2).[1]

Other coagulation factors that undergo inhibition by UFH are factors IXa, XIa, and XIIa. Unfractionated heparin also blocks thrombin-induced activation of factors V and VIII and enhances the release of tissue factor pathway inhibitor, which reduces the procoagulant activity of the tissue factor VIIa complex (Figure 3).[1, 2] Once UFH has accelerated the activity of an antithrombin molecule, it can dissociate and accelerate the activity of additional antithrombin molecules, thereby providing a continuing anticoagulant effect. Unfractionated heparin has no fibrinolytic activity and will not lyse existing clots.

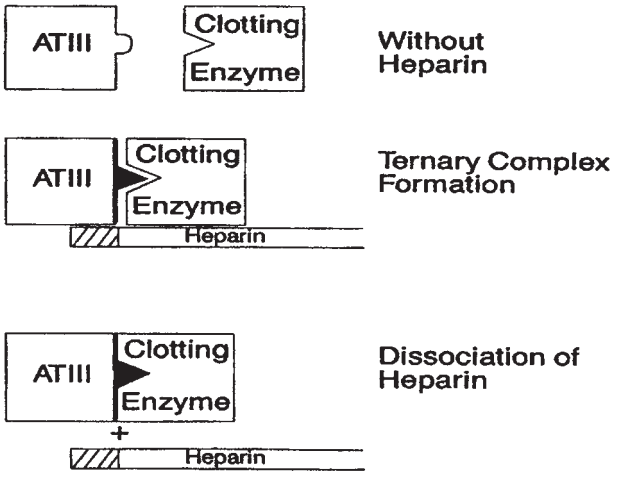

Figure 1. Inactivation of clotting enzymes by unfractionated heparin. AT = antithrombin. (From reference 1 with permission.)

Pharmacologic and Pharmacokinetic Limitations of UFH

The actions of UFH described above, together with its short half-life and reversibility by protamine, appear to make it a useful agent for treating acute thromboembolic conditions. However, a number of limitations have been identified, both pharmacologic and pharmacokinetic.

Being entirely dependent on antithrombin, UFH is an indirect anticoagulant. The antithrombin-heparin complex is relatively large and unable to inactivate thrombin that is bound to the fibrin clot. Since such thrombin retains its procoagulant activity, UFH may be limited in its ability to prevent clot propagation and extension.[1]

The binding of UFH to a wide variety of cells and plasma proteins has significant clinical implications. For example, this binding is a major factor leading to the reduced bioavailability seen with UFH, especially when prescribed at lower doses or given subcutaneously. In addition, the binding of heparin to platelets and endothelial cells may contribute to increased bleeding events. The inhibition of both platelet and clotting activation is a desirable attribute for a systemic anticoagulant. Paradoxically, however, UFH actually may induce platelet activation through its interaction or binding with platelet

Figure 2. Unfractionated heparin inactivation of thrombin versus factor Xa. AT = antithrombin. (From reference 1 with permission.)

factor 4. The binding of heparin to platelet factor 4 is thought to be responsible for one of the most serious heparin-related complications, heparin-induced thrombocytopenia (HIT).[3]

Unfractionated heparin also has the undesirable property of releasing von Willebrand's factor (vWF) from the blood vessel wall.[4] This activity is more variable with low-molecular-weight heparins, depending on the specific agent. In patients with unstable angina, for example, an early increase in vWF, at least partly induced by UFH, may be a risk factor for an adverse outcome. Binding of UFH to vWF may interfere with vWF-dependent platelet function.

Unfractionated heparin is difficult to dose and monitor due to its variable and unpredictable pharmacokinetics. To further complicate matters, the test most commonly used to monitor its effect and adjust therapy, the aPTT, is also variable as well as unreliable.

The unpredictable bioavailability of UFH is due in part to its initial rapid clearance from the blood through a saturable process that involves binding to endothelial cells, macrophages, and acute phase reactants such as platelet factor 4. Once the mechanisms of rapid clearance are saturated, the elimination of UFH becomes dependent on a much slower renal process.[1] As a result, initial intravenous doses or lower subcutaneous doses quickly disappear from the circulation due to the rapid binding described earlier. As clearance becomes dependent on the slower renal mechanism, increased UFH dosing or continued administration provides a disproportionate increase in both the intensity and the duration of the anticoagulant effect. For example, lower doses such as 25 U/kg have an apparent half-life of 30 minutes, whereas higher doses of 100 and 400 U/kg are associated with half-lives of 60 minutes and 150 minutes, respectively.[1]

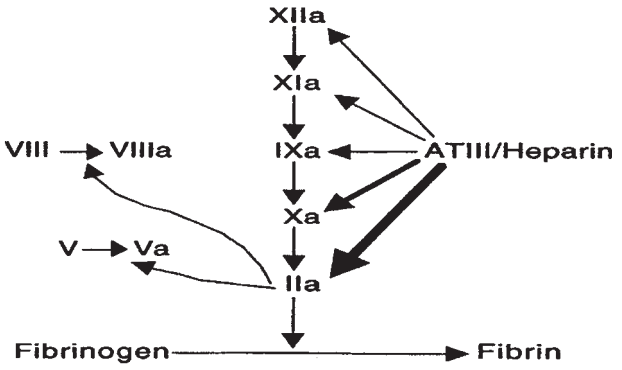

Figure 3. Clotting factor inhibition by the heparin-AT complex. AT = antithrombin. (From reference 1 with permission.)

In addition, substances such as platelet factor 4 and other acute-phase reactants that bind and inactivate UFH during an acute thrombotic event may disappear once the acute clotting process has been suppressed. As a result, these complex pharmacokinetics make it very difficult to achieve an early therapeutic effect with UFH and require continued frequent monitoring to avoid overanticoagulation or underanticoagulation as the clearance and level of inactivating substances change.

aPTT: Limitations in Practice

The UFH dose is usually carefully and frequently titrated against the aPTT. However, specific problems with this coagulation test raise concerns pertaining to its ability to guide UFH dosage adjustments. The difficulty in dosing UFH appropriately has critical clinical significance. In one report, failure to achieve an adequate therapeutic heparin concentration early in the treatment of an acute thrombotic event was associated with a 6–20-fold increase in recurrence rates in patients with deep vein thrombosis or myocardial infarction.[1]

A 1993 study demonstrated that therapeutic aPTT values could be achieved more readily with the use of a weight-based dosing nomogram than with standard dosing.[5] The same study also demonstrated that the risk of recurrent deep vein thrombosis was reduced by approximately 80% (5% weight-based dosing vs 25% standard dosing) among patients who achieved an adequate aPTT within 48 hours. The study's nomogram subsequently was widely adopted but, unfortunately, often without the realization that the guiding aPTT values (and therefore the nomogram) were valid only at the institution where the nomogram was developed. This was due in part to variations in reagent sensitivity, laboratory equipment, and procedures. As a result, other institutions that adopt the nomogram need to determine their own target aPTT range and adjust the nomogram accordingly.

This problem was highlighted in another 1993 report,[6] which described a wide range of variation in the sensitivity of reagents used to measure the aPTT. To resolve this issue, attempts have been made to identify a method to standardized the aPTT in a manner analogous to the international normalized ratio (INR) for

Table 1. aPTT Therapeutic Ranges for Representative Modern Thromboplastin Reagents, Determined by a Validated Method

Year	Reagent	aPTT (sec)	aPTT Ratio
1989	Actin FS	60–85	1.8–2.5
1991	Actin FS	79–105	2.3–3.0
2001	Actin	49–92 to 49–109	1.9–3.7 to 2.1–4.6
2001	Actin FS	72–119 to 98–165	2.6–4.3 to 3.7–6.2
2001	Actin FSL	57–98 to 84–124	2.1–3.5 to 2.5–3.8
2001	IL test	49–109 to 63–101	1.7–3.8 to 1.9–3.3
2001	Thrombosil I	44–75 to 58–112	1.6–2.7 to 2.4–4.5

aPTT = activated partial thromboplastin time; FS = factor sensitivity; FSL = factor sensitive and lupus sensitive; IL = instrument laboratories.
Adapted from reference 9.

monitoring oral anticoagulants. However, even when studies used few aPTT reagents, efforts at standardization were only partially successful. As a result, aPTT standardization is unlikely to occur in the near future.[7]

These issues led to the 1995 recommendation of the American College of Chest Physicians that every laboratory should define its own therapeutic aPTT range. This range should be based on correlations performed between the aPTT and heparin serum concentrations using the individual laboratory's aPTT reagent-equipment combination.[8]

The degree of heparin sensitivity of an aPTT assay apparently has become even more significant in recent years as more sensitive reagents have become available.[9] A 2003 review found that therapeutic aPTT ratios often must be substantially higher than the traditional value of 1.5 in order to reflect therapeutic concentrations of heparin (Table 1). In fact, the lowest therapeutic aPTT ratio was 1.6, whereas the upper limit of the range was as high as 6.2. Clearly, an aPTT ratio range of 1.5–3.0 times control no longer can be considered a valid universal therapeutic range.

Although the process of having each laboratory determine its own target aPTT range would seem to correctly adjust the therapeutic aPTT target for a given institution, this process has been problematic. As demonstrated in one report, the correlation between aPTT values and heparin serum concentrations is not "tight."[10] The investigators defined the target aPTT range by correlating heparin serum concentrations with aPTT values and then tested the target aPTT range prospectively. Only 82% of so-called therapeutic aPTT values actually indicated heparin concentrations in the therapeutic range.

Accurate aPTT monitoring is further complicated by significant but variable interference from warfarin. In one study, warfarin treatment in patients with INR values of 2–4 caused an elevation in the aPTT of approximately 20–60 seconds.[11] Presumably, the degree of warfarin interference with the aPTT varies with the sensitivity of different aPTT reagents.

In summary, the unpredictable and variable pharmacokinetics of UFH make appropriate dosing highly difficult. Failure to achieve an early therapeutic heparin effect is associated with a several-fold increase in recurrence rates of thromboembolism. Also, the aPTT assay is a variable and poorly reproducible test that is influenced by reagent sensitivity, laboratory equipment, and interacting drugs.

Drug-Related Problems with Heparin: Beyond Bleeding

Immune-mediated HIT is a serious complication of heparin therapy that results from antibodies formed against the heparin–platelet factor 4 complex. Through mechanisms that are incompletely understood, HIT induces a prothrombotic state involving a significant increase in thrombin production, platelet aggregation, and platelet activation that can produce venous or arterial thrombosis. Platelet activation is thought to potentiate the process by releasing microgranules that stimulate thrombin production. This, in turn, potentiates further platelet activation. Similarly, activated platelets release additional platelet factor 4 that can neutralize heparin. When this highly prothrombotic state is suspected, heparin should be withdrawn immediately, and therapy with a nonheparin direct thrombin inhibitor should be started.

Even with appropriate therapy, however, approximately 9–22% of patients with HIT will die, and an additional 6–18% will require amputation or experience another thromboembolic event.[12] Finally, HIT can develop as late as

several weeks after a completed course of UFH therapy. One report described 14 cases of delayed HIT that occurred 19–40 days after administration of a form of heparin.[13] Of the 14 patients, 11 who received therapy to treat newly identified thrombotic events all rapidly worsened, and three died. The catastrophic nature of this condition mandates its consideration whenever a patient experiences a new thrombosis after a recent course of heparin therapy.

Conclusion

From a historic perspective, the availability of heparin in the 1940s proved to be the best—if not the only—effective therapy for millions of patients who experience a life-threatening thromboembolic event each year in the United States. Perhaps no other drug has provided so much benefit to so many patients for more than half a century without being challenged by newer and better agents. Even so, serious limitations to the safe and effective use of UFH are not shared by alternative anticoagulation agents developed over the past 10 years. In fact, were it not for the difference in cost of these newer agents, one might well conclude that UFH is a truly excellent drug whose time has come…and gone.

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