HEPARIN THERAPY: STANDARD VS WEIGHT-BASED DOSING NOMOGRAM

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IN 1916 A MEDICAL STUDENT named McLean, while investigating the nature of ether-soluble procoagulants, also discovered a phospholipid anticoagulant. Soon thereafter, a water-soluble mucopolysaccharide, named heparin because of its abundance in the liver, was discovered by Howell (1922), in the same laboratory that McLean had been working. The use of heparin in vitro to prevent the clotting of shed blood eventually led to its use in vivo to treat venous thrombosis. In addition to its anticoagulant effects, heparin inhibits platelet function and increases the permeability of vessel walls. Heparin also inhibits the proliferation of vascular smooth-muscle cells and delayed hypersensitivity reactions. This review will focus on the anticoagulant effects of heparin, with special emphasis on the weight-based heparin-dosing nomogram.

Biochemistry and Mechanism of Action of Heparin

Heparin is an anionic, sulfated glycosaminoglycan, composed of chains of alternating residues of D-glycosamine and a uronic acid. Its major anticoagulant effect is accounted for by a unique pentasaccharide, with a high-affinity binding sequence to antithrombin III (ATIII). The unique sequence is present in only one third of heparin molecules. The anticoagulant effect of heparin is mediated largely through its interaction with ATIII. This produces a conformational change in ATIII and so markedly accelerates its ability to inactivate the coagulation enzymes thrombin (factor IIa), factor IXa, Xa, XIa, and factor XIIa. Of these enzymes, thrombin is the most sensitive to inhibition by heparin! ATIII.

Heparin catalyzes the inactivation of thrombin by ATIII by acting as a template to which both the enzyme and inhibitor bind to form a ternary complex. In contrast, the inactivation of factor Xa by ATIII/heparin complex is achieved by binding the enzyme to ATIII only and does not require ternary complex formation. Heparin molecules that contain fewer than 18 saccharides are unable to bind thrombin and ATIII simultaneously, but retain their ability to catalyze the inhibition of factor Xa by ATIII. Heparin also catalyzes the inactivation of thrombin by a second plasma cofactor, heparin cofactor II. This second anticoagulant effect of heparin is specific for thrombin; it does not require the unique ATIII-binding pentasaccharide, and it is achieved only at very high doses of heparin.

Heparin is heterogeneous with respect to molecular size, anticoagulant activity, and pharmacokinetic properties. The molecular weight of heparin ranges from 5,000 to 30,000 with a mean molecular weight of 15,000. The anticoagulant activity of heparin is heterogeneous because of the following: (1) only one third of the heparin molecules administered to patients have...
HEPARIN THERAPY

anticoagulant activity; (2) the anticoagulant profile of heparin is influenced by the chain length of the molecules; and (3) the clearance of heparin is influenced by its molecular size, with the higher molecular-weight species being cleared from the circulation more rapidly than the lower molecular-weight species. This differential clearance phenomenon results in an accumulation in vivo of the lower molecular-weight species that have a reduced ratio of antithrombin to anti-factor Xa activity. This effect is responsible for the differences observed when the relationship between the heparin level and the activated partial thromboplastin time (APTT) is assessed in vivo and in vitro, since the lower molecular-weight species that are retained in vivo are measured in the anti-factor Xa heparin assay but have minimal effects on the APPT.11

Administration, Pharmacokinetics, and Pharmacodynamics

Heparin is poorly absorbed from the gastrointestinal tract and, therefore, must be given by injection. The two preferred routes of administration are intravenous and subcutaneous. Intramuscular injection can produce large hematomas caused by accidental puncture of an intramuscular vein and, therefore, should be avoided. There is evidence that heparin administered by intermittent injection is associated with more bleeding than when it is administered by the continuous intravenous route.2 The latter method is, therefore, preferred if heparin is administered intravenously. The efficacy and safety of heparin administered by either the continuous intravenous method or by the subcutaneous route are comparable, provided that the dosages used are adequate.2,12 If, however, the subcutaneous route is selected, the initial dose must be sufficiently high to counteract the reduced bioavailability that occurs when heparin is administered by the subcutaneous route.13 If an immediate anticoagulant effect is required and heparin is administered by subcutaneous injection, the initial dose should be accompanied by an intravenous bolus injection because an anticoagulant effect from subcutaneous heparin is delayed for 1 to 2 h.

The pharmacokinetics of heparin are complicated and incompletely understood. Following its injection and passage into the bloodstream, heparin binds to a number of plasma proteins, including histidine-rich glycoprotein, platelet factor IV (PFIV),14 vitronectin,15 fibronectin,16 and von Willebrand factor (VWF).17 The binding of heparin to these proteins contributes to its reduced plasma bioavailability at low concentrations, to the variability of the anticoagulant response to fixed doses of heparin in patients with thromboembolic disorders,15 and to the laboratory phenomenon of heparin resistance.11

Heparin also binds to endothelial cells and macrophages,19 a property that contributes to its complicated pharmacokinetics. Heparin is cleared through a combination of a rapid saturable and a much slower first-order mechanism of clearance.20 The saturable phase of heparin clearance is thought to be due to heparin binding to receptors on endothelial cells and macrophages19 where it is internalized into smaller and less sulfated forms.21 Clearance through the slower nonsaturable mechanism is largely renal. At therapeutic doses, a considerable proportion of the administered heparin is cleared through the rapid saturable, dose-dependent mechanism of clearance. Because of these kinetics, the anticoagulant response to heparin at therapeutic doses is not linear but increases disproportionately, both in its intensity and duration with increasing dose. Thus, the apparent biologic half-life of heparin increases from approximately 30 min with an intravenous bolus of 25 U/kg to 60 min with an intravenous dose of 100 U/kg and to 150 min with a bolus of 400 U/kg.20,22

The plasma recovery of heparin is reduced when the drug is administered by subcutaneous injection in low doses (eg, 5,000 UI/2 h) or moderate doses of 12,500 UI/2 h or 15,000 UI/12 h.13,23 However, at high therapeutic doses of heparin (>35,000 U/24 h), the plasma recovery is almost complete.12 The poor bioavailability of heparin when administered by subcutaneous injection occurs because as heparin enters the intravascular space slowly from subcutaneous depots, it binds to saturable sites on endothelial cells and macrophages where it is internalized and metabolized. Circulating plasma levels are achieved only after these cell surface receptors are saturated, either by a large loading dose or by the cumulative effects of a number of moderately high doses.13
Modification of the Anticoagulant Effect

The anticoagulant effect of heparin is modified by platelets, fibrin, vascular surfaces, and plasma proteins. Platelets inhibit the anticoagulant effect of heparin by binding factor Xa and protecting it from inactivation by the heparin-antithrombin III complex and by secreting the heparin-neutralizing protein platelet factor IV.

Fibrin binds thrombin and protects it from inactivation by the heparin-antithrombin III complex. In plasma, approximately 20 times more heparin is needed to inactivate fibrin-bound thrombin than to inactivate free thrombin. The relative resistance of fibrin-bound thrombin to inhibition by heparin may explain why the extension of venous thrombosis requires higher concentrations of heparin than preventing its formation, as well as why heparin fails to inhibit thrombin activity after successful coronary thrombolysis in some patients.

Thrombin bound to subendothelial surfaces is also protected from inactivation by heparin, possibly through mechanisms similar to those that protect fibrin-bound thrombin.

Heparin binds to many proteins, of which three - histidine-rich glycoprotein, platelet factor IV, and vitronectin - also neutralize its anticoagulant activity. Elevated levels of these proteins may contribute to heparin resistance in patients with inflammatory and malignant disorders. Antithrombin III deficiency, although rare, may render a patient refractory to heparin therapy.

There are reports of physical interactions between heparin and other drugs. Recent studies have suggested that intravenous nitroglycerin (NTG) induces heparin resistance and that larger doses of heparin are needed to maintain anticoagulation in the therapeutic range. Although the exact mechanism of this possible interaction is still unclear, current evidence suggests that NTG induces an antithrombin III abnormality that changes heparin's anticoagulant activity. In contrast, other researchers have reported that NTG has no effect on heparin's anticoagulant activity.

Laboratory Monitoring and Dose-Response Relationships of Heparin

The anticoagulant effects of heparin are usually monitored by the APTT, a test that is sensitive to the inhibitory effects of heparin on thrombin, factor Xa, and factor IXa. When heparin is administered in fixed doses, the anticoagulant response to heparin varies among sick patients, including those with acute venous thromboembolism and with myocardial ischemia. This variability is caused by differences between patients in their plasma concentrations of heparin-neutralizing plasma proteins and in their rates of heparin clearance. A relationship exists between the clinical effectiveness of heparin and its effect on the APTT for the following conditions: prevention of recurrent thrombosis in patients with proximal-vein thrombosis, prevention of mural thrombosis in patients with acute myocardial infarction, prevention of recurrent ischemia in patients following streptokinase therapy for acute myocardial infarction, and prevention of coronary artery reocclusion after thrombolytic therapy with tissue plasminogen activator. For this reason, the dose of heparin administered to patients should be monitored by laboratory testing and adjusted to achieve a therapeutic level. This anticoagulant effect is referred to as the "therapeutic range."

The recommended therapeutic range for APTT for the treatment of venous thrombosis is based on a study performed in rabbits which demonstrated that thrombus extension was prevented by a heparin dose that prolonged the APTT ratio from 1.5 to 2.5 compared to baseline, corresponding to a heparin level by protamine titration of 0.2 to 0.4 U/mL.

Unfortunately, the different commercial APTT reagents vary in their responsiveness to heparin. This has been attributed to the technical variables that affect the APTT response to heparin which include the type of clot detection system, the contact activator, and the phospholipid composition of the reagent. Important variations in the responsiveness to heparin between different batches of the same brand of APTT reagent have also been reported. An ideal APTT system should give a linear relationship over a clinically relevant anticoagulant range. Efforts are being made to develop standards for the APTT system, but an international standard is not yet available. Until there is a reliable system of APTT standardization for heparin monitoring, therapeutic ranges should be established in each local laboratory. An approximation of the therapeutic range of 0.2 to 0.4 U/mL of heparin (by protamine titration) can be
made by testing the Am reagent in a plasma system that has been calibrated by the addition of a range of clinically relevant concentrations of heparin. 11

Although there is good evidence that APIT ratios above the lower limit of the therapeutic range are associated with protection against thrombosis,13,23,42-44 maintaining the APIT in the therapeutic range does not guarantee protection from bleeding complications.48

Heparin Dosing

Prevention of Venous Thrombosis

Less intense anticoagulant effect is required to prevent venous thrombosis with heparin than to treat established thrombosis. Low-dose heparin, 5,000 IU subcutaneously two or three times daily, is highly effective in preventing venous thrombosis in moderate-risk patients and is administered without laboratory monitoring. However, in very high-risk patients such as those having hip surgery, the incidence of thrombosis is approximately 25% and of proximal-vein thrombosis it is 10% to 15%, despite low-dose heparin prophylaxis.49 The efficacy of the fixed, low-dose heparin therapy following hip surgery is improved without compromising safety by adjusting the dose to achieve a minimal heparin effect. The APIT was prolonged slightly (APIT ratio, 1.1 to 1.2 compared to baseline) which required a mean daily dose of heparin in excess of 18,000 IU.50 The adjusted dose regimen has limitations for routine use since it requires careful monitoring and the use of a responsive APIT system. Nevertheless, the study results illustrate the important principle that a small heparin effect by ex vivo measurement is required for optimal prophylaxis in very high-risk patients.

Treatment of Established Thrombosis

Heparin is the anticoagulant-of-choice when a rapid anticoagulant effect is required. It has an immediate onset of action after intravenous (IV) administration. Heparin is indicated for the treatment of venous thromboembolism, for the early treatment of patients with unstable angina and acute myocardial infarction, in patients who have cardiac surgery under cardiac bypass, and who have vascular surgery.11 Heparin is not considered as a thrombolytic agent but an agent that prevents further thrombosis while auto-thrombolysis occurs.

Traditional Dosing

Literature review reveals that the determination of appropriate heparin dosing is often problematic. The size of initial bolus dose varies; in some cases bolus doses are omitted, while the initial rates of heparin infusion appear inconsistent and extended periods of time are required to obtain a therapeutic APIT.51 Physician' dosing decisions vary widely, as do their therapeutic goals. Practice audits reveal frequent underdosing, with delays in achieving therapeutic anticoagulation leading to suboptimal clinical outcome. Clarification of treatment goals and specific dosing guidelines may improve outcomes.52 Hull and colleagues13 report that a rapidly exceeding "therapeutic threshold" (APIT, 1.5 times the control) reduces the rate of recurrent thromboembolism from 25% to 2%, a finding confirmed in other studies.53 In addition, a retrospective analysis of initiation of anticoagulant therapy suggests that an initial heparin infusion dose of 1,000 IU/h is often insufficient.54,55

A review of the initiation of anticoagulant therapy in patients with deep-vein thrombosis (DVT) and/or pulmonary embolism (PE) in Australia reveals that only 68% of patients received an IV loading dose of heparin. Only 21% of patients had a therapeutic APIT after 24 h and 44% after 48 h of therapy with heparin, with most results (60.3%) of APIT being below the therapeutic range.55 It is generally recommended that a loading dose of heparin should be given to all patients requiring anticoagulation.

Intravenous heparin therapy appears to maintain early patency of infarction-related blood vessels in patients with acute myocardial infarction treated with recombinant tissue-plasminogen activator (rtPA). Because the risk of reocclusion is high within the first 48 h, heparin is usually administered as a bolus infusion (5,000 IU) at the time of thrombolytic therapy, and treatment is continued at an initial rate of 1,000 IU/h and titrated to maintain the APIT at 1.5 to 2 times the baseline (control) value. Adequate anticoagulation is crucial in these patients since sub-therapeutic APTT values have been associated with lower patency rates.56 The optimal upper limit for the therapeutic range has not been identified. There is concern that higher doses of heparin will be associated with more bleeding complications,2 but the association of high APIT with hemorrhagic events is not a consistent finding.57
Unfortunately, randomized controlled studies have not compared higher initial heparin doses with 1,000 U/h, and many physicians continue to follow this clinical tradition.

Standard Heparin-Dosing Nomogram

The use of a heparin nomogram has been proposed in the treatment of acute venous thromboembolism to streamline therapy and to prevent periods of inadequate anticoagulation. The recently completed TIMI-4 study compared three thrombolytic treatment regimens for acute myocardial infarction in conjunction with IV heparin bolus of 5,000 U, followed by 1,000 U/h. A heparin-dosing nomogram was developed to maintain the therapist APPT at 1.5 to 2 times the baseline (control) value. Sub-therapeutic APPT values were noted in 29%, and 46% at 24 h and 48 h, respectively, after heparin treatment was begun.

Patients with sub-therapeutic values were younger and weighed more than patients with therapeutic values. The authors concluded that weight-adjusted heparin dosing may provide further improvement in anticoagulation with heparin therapy. The study results also recommended that, it is most appropriate not to change the heparin infusion, even if the APPT prolongation is above the normal therapeutic range for up to 6 to 12 h after rtP A has been withdrawn, as its effects on APPT will usually dissipate, and accurate heparin infusion changes can be made after that time. 51

In an attempt to standardize heparin therapy and reduce delays in achieving and maintaining a therapeutic APPT result in patients with venous thromboembolism, Cruickshank et al58 developed a heparin dosage adjustment nomogram. All patients received an IV bolus of 3,000 U of heparin, followed by a continuous infusion of 1,280 U/h. The proportion of patients in the nomogram group who achieved a therapeutic APPT (1.5 to 2.5 times the baseline) at 24 h after initiation of heparin therapy was 66% (compared to 37% for historical control) which increased to 81% at 48 h (compared to 58% for control). The mean time to achieve the targeted therapeutic APPT in the nomogram patients was 24.3 ± 2.4 h compared with 56.9 ± 6.4 h for the control group. Thus, the use of heparin nomogram resulted in achieving a therapeutic APPT at 24 and 48 h in a large proportion of patients and reduced period of inadequate anticoagulation and over-anticoagulation during heparin therapy. Similar results using similar nomogram have been reported recently.59 There were more APPT tests performed in the nomogram group. The nomogram removed some of the inherent delays in decision-making once a laboratory result was available. Elimination of the delay between the arrival of the results and contact with the treating physician increased nurses' efficiency. The mean duration of hospital stay was not different between groups. However, to reduce the length of the hospital stay, it may be necessary to add a structured warfarin protocol.59

Patient-Specific Nomogram

Identification of a valid patient-specific variable as basis for heparin dosage adjustment and maintenance of therapeutic APPT value was recently studied by Gunnarsson et al60 in patients with cardiovascular disease. Linear regression models were used to define the relationship between heparin infusion rate used at the time the patient's APPT was first noted to be in the therapeutic range and selected patient-specific variable. The statistical model that best explained the quantitative relationship between infusion rate and a patient-specific variable involved blood volume (r² = 0.3756). Similar, although somewhat weaker, relationships were noted between infusion rate and the use of total body weight (TBW) and height (r² = 0.3455), between infusion rate and body surface area (r² = 0.3430), and between infusion rate and TBW alone (r² = 0.3043). The use of ideal body weight resulted in weaker relationships and height did not show statistical significance. When referenced to TBW, a mean initial infusion rate of 13.1 U/kg/h was associated with achieving a therapeutic APPT. Because of the easy usage of this variable, a loading dose of 75 U/kg followed by an initial infusion rate of 13 U/kg/h were recommended in phase 2 of the study. All subsequent dosage adjustments were done according to the weight-based nomogram. A higher percentage (77.8%) of patients reached a therapeutic APPT within the important first 24 h of therapy (77.8% for nomogram group, 54.4% for empiric heparin dosing). A significant reduction in the time required to achieve therapeutic APPT (13.1 ± 11.9 h for nomogram group, 20.7 ± 19.1 h for empiric group) was achieved. Over-therapeutic APPT was reported in 2.2% of the nomogram group (compared with 10.2% for empiric group) while
HEPARIN THERAPY

sub-therapeutic Am was reported less frequently in the nomogram group. However, the performance of the nomogram in the maintenance of therapeutic APTT after it was first achieved was not evaluated.

Weight-based vs Standard-care Nomogram

In a randomized controlled trial by Rachke et al.,53 the weight-based heparin-dosing nomogram was compared to a "standard-care" nomogram that had previously been recommended by the American College of Chest Physicians. 54 The former group received 80 U/kg (TBW) heparin bolus followed by an initial IV infusion rate of 18 U/kg/h, rounded to the nearest 100 U. APTT was measured every 6 h with subsequent heparin-dosage adjustment according to a TBW-based heparin-dosing nomogram. The therapeutic threshold was achieved in 86% of patients in the weight-based group on the first Am drawn during therapy (compared with 32% in the standard-care group, P < 0.001). By 24 h, the proportion exceeding the therapeutic threshold was 97% in the weight-based group (compared with 77% of the control group, P < 0.002). The mean time required to exceed the therapeutic threshold was 8.2 h in the weight-based group and 20.2 h in the standard-care group (P <0.001). The mean duration before reaching an Am value within the therapeutic range was 14.1 h in the weight-based group (compared with 22.3 h in the standard-care group, P < 0.003). In the weight-based group, 5% had recurrent venous thromboembolism compared with 25% in the standard-care group, yielding a relative risk of 5. The incidence of minor bleeding was generally low and not different (3.2% of the weight-based vs 3.8% of the standard-care group), while major bleeding was reported in only one patient in the standard-care group. 53

Conclusion

The weight-based heparin nomogram is widely generalizable and has proven to be effective, safe, and superior to one based on standard practice. The superior performance of the weight-based heparin-dosing nomogram is due to the fact that it calculates patient-specific heparin doses that approximate the optimum dose for each individual. The weight-based nomogram prescribes initial doses closer to eventual heparin requirements, drives sub-therapeutic Am results above the therapeutic threshold more rapidly, and requires fewer dose adjustments to maintain Am results within the therapeutic range. The incidence of major bleeding using the weight-based nomogram is much lower than previously reported with "standard-care" nomogram. Rapidly exceeding the therapeutic threshold within the first 24 h in the majority of patients reduced the incidence of recurrent thromboembolism among patients on the weight-based heparin-dosing nomogram. On the basis of the performance of the weight-based nomogram, King Khalid University Hospital, in Riyadh, has adopted it as the standard of practice.

Physicians’ reluctance to use the nomogram seems to be owing primarily to lack of familiarity rather than lack of confidence in the nomogram. It is possible that having the nomogram preprinted on the physician drug order forms would make use of the nomogram easier, eliminate inter-physician and intra-physician variability in heparin dosing, and would encourage more widespread usage. It would also remove some of the inherent delays in decision-making once laboratory results are available.

Each institution may need to customize the nomogram's APTT ranges for local use in one of two ways: APTT values may be standardized by comparing them with other measures of heparin activity (anti-factor Xa activity or protamine titration), or a more practical but less accurate alternative involves the use of Am ratios (actual Am/baseline APTT).

References


