Theme Issue Article

Monitoring unfractionated heparin with the aPTT: Time for a fresh look

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Summary

Laboratory monitoring is widely recommended to measure the anticoagulant effect of unfractionated heparin and to adjust the dose to maintain levels in the target therapeutic range. The most widely used laboratory assay for monitoring unfractionated heparin therapy is the activated partial thromboplastin time (aPTT). A fixed therapeutic range for the aPTT of 1.5 to 2.5 times the control value has become widely accepted, but the evidence supporting this range is weak and the clinical validity of using the aPTT for predicting thrombotic or bleeding events is questionable. The aPTT test is also affected by numerous pre-analytic and analytic variables that are unrelated to the anticoagulant effect of unfractionated heparin, further eroding its potential value for monitoring unfractionated heparin treatment. Unfractionated heparin dose appears to be more important than the aPTT in predicting clinical efficacy. Despite serious limitations, the reliance on the aPTT is likely to continue because of its ready availability and familiarity of clinicians with the test. The focus of clinicians who manage unfractionated heparin therapy should be to ensure that an adequate starting dose of unfractionated heparin is used and that the aPTT method is standardized. Future research efforts should be directed towards developing methods to improve standardization of the aPTT assay for monitoring unfractionated heparin. Direct measures of the concentration of unfractionated heparin in the blood are attractive because these assays are not affected by many of the biologic variables that interfere with the aPTT and may be suitable for automation. However, currently available unfractionated heparin assays are much more expensive than the aPTT, are not widely available, and their validity has not been adequately assessed in clinical outcome studies.

Keywords

Heparin, laboratory monitoring, aPTT

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Introduction

Unfractionated heparin was introduced into clinical practice more than 50 years ago and remains widely used because it is an effective, inexpensive, and a relatively safe anticoagulant (1). Although unfractionated heparin has been replaced by low-molecular-weight heparin (LMWH) for many indications, it remains the anticoagulant of choice among selected patient groups because of its short half-life, its greater safety in patients with renal failure, and its ability to have its anticoagulant effect reversed by protamine sulphate (1). Both unfractionated heparin and LMWH achieve their anticoagulant effect by binding to antithrombin and accelerating antithrombin-dependent inhibition of thrombin and coagulation factors IX, X, XI, and XII (2, 3). Compared to LMWH, unfractionated heparin exhibits a more marked variability in anticoagulant response among individuals. This variable and unpredictable between-individual response to unfractionated heparin is caused, at least in part, by non-specific binding of the strongly negatively-charged polysaccharide chains to positively-charged plasma proteins, many of which are acute phase reactants, and by non-specific binding of unfractionated heparin chains to platelets and activated endothelial cells (4, 5). Since it is widely believed that failure to achieve adequate unfractionated heparin levels impairs its antithrombotic efficacy and that high unfractionated heparin levels can cause excessive bleeding, laboratory monitoring is recommended to measure the anticoagulant effect of unfractionated heparin and to adjust the dose to maintain levels in the target therapeutic range (1, 6).

The most widely used laboratory assay for monitoring unfractionated heparin therapy is the activated partial thromboplastin time (aPTT). A therapeutic range for the aPTT of 1.5 to 2.5 times the control value has become widely accepted, but the evidence supporting this range is weak and the clinical validity of using the aPTT for predicting thrombotic or bleeding events has

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been questioned (1, 6, 7). The aPTT test is also affected by numerous pre-analytic and analytic variables that are unrelated to the anticoagulant effect of unfractionated heparin, further eroding its potential value for monitoring unfractionated heparin treatment.

This paper reviews the ideal characteristics of a laboratory assay to measure the anticoagulant effect of anticoagulant drugs and critically examines the role of the aPTT for monitoring the anticoagulant effect of unfractionated heparin according to these criteria.

Ideal characteristics of a laboratory assay to monitor anticoagulant drugs

The goal of laboratory monitoring of anticoagulant therapy is to select a dose which achieves an optimal anticoagulant effect, thereby preventing thrombus formation or progression while minimizing the risk of bleeding. In the absence of a direct measure of the physiologic effect of the anticoagulant (e.g. prevention of thrombus growth), a secondary measure (e.g. aPTT, INR) is used as a proxy or surrogate measure for thrombosis and bleeding (6). The use of the INR as a surrogate for efficacy and safety of vitamin K antagonists is well established. Can the same be said for the aPTT and unfractionated heparin?

In the context of the aPTT for monitoring unfractionated heparin therapy the test (aPTT) should ideally have the following characteristics (6, 8).

- The assay result should have a well-defined and preferably linear relationship with clinical outcome (recurrent thrombosis and bleeding)
- The assay should have good precision and be well-standardized among laboratories and assay reagents.
- The assay should be readily available and inexpensive.

The aPTT should have a well-defined relationship with clinical outcome (recurrent thrombosis and bleeding)

The common use of a therapeutic range of 1.5 to 2.5 is based on a post-hoc analysis of a descriptive clinical study published in 1972 by Basu et al. at McMaster University (9) in which it was reported that unfractionated heparin doses that prolonged an aPTT to 1.5–2.5 times control were associated with a reduced risk for recurrent thromboembolism. At about the same time, Chiu et al. (10), also from the McMaster Group, demonstrated that an aPTT level of 1.5–2.5 times control prevented extension of established experimental thrombi in rabbits. Based on the concordance of these clinical and experimental findings, an aPTT therapeutic range of 1.5–2.5 times control subsequently gained wide acceptance. Additional studies using the "McMaster thromboplastin reagent" showed that this range corresponded to an unfractionated heparin level of 0.2 to 0.4 IU/ml by protamine titration and of 0.3 to 0.7 IU/ml by anti-Xa assay (1). Other subgroup analyses of clinical studies appeared to support an association between an aPTT less than 1.5 times control and recurrent thrombosis (11–14), and an increased risk of recurrent thrombosis was reported among patients who did not achieve a therapeutic aPTT level within 24 or 48 hours of commencing unfractionated heparin (12, 15, 16). There were also reports of a relationship between unfractionated heparin concentrations in excess of 0.7 or 0.8 anti-Xa IU/ml and bleeding (17, 18), although the data supporting an association between over-anticoagulation and bleeding were less secure.

As more experience from prospective studies evaluating unfractionated heparin in the treatment of thrombotic disease began to emerge, it became clear that unfractionated heparin was effective for the treatment of venous thromboembolism (VTE), provided that treatment was started with an adequate dose (at least 5,000 units as a bolus followed by 30,000 units per 24 hours by continuous intravenous infusion) (19–21). Although the aPTT was used to monitor the unfractionated heparin dose, different aPTT reagents were used, so the anticoagulant effects associated with a target aPTT ratio of 1.5 to 2.5 would have differed considerably among studies (22). Based on the foregoing observations, the alleged association between a lower threshold aPTT of 1.5 times control and recurrent venous thrombosis was re-examined. Anand et al. (23) performed a meta-analysis of five studies that provided information on the relation between the risk of recurrent VTE and the APTT response to unfractionated heparin when the drug was initiated as a bolus followed by a continuous intravenous infusion of at least 30,000 IU/24 h. The overall recurrence rate was 6.3% in patients whose APTT results were subtherapeutic (<1.5 times control) for the first 24 to 48 hours and 7% in patients whose APTT results were above the lower limit of the therapeutic range (OR 0.89; 95% CI: 0.2 to 4.0), thereby questioning the earlier evidence that the risk of recurrent venous thromboembolism is dependent on achieving a therapeutic APTT result at 24 to 48 hours in patients who are treated with a bolus of unfractionated heparin followed by a continuous intravenous infusion of at least 30,000 IU/24 h. Similar results were obtained from a subsequent individual patient meta-analysis by Anand et al. of three studies involving 961 patients with acute deep vein thrombosis who received a 5,000-IU bolus of intravenous unfractionated heparin followed by an infusion of 1,250 to 1,280 IU/hr (24). The risk of recurrence was 6.7% in the subtherapeutic group compared with 5.3% in the group who had a therapeutic aPTT at 24 hours, a 30% relative increase which was not statistically significant (RR 1.30; 95% CI: 0.64 to 2.63) (24). The latter study was, however, underpowered and did not exclude the possibility that there was a small but significant increase in the risk of recurrent thrombosis among patients with a subtherapeutic aPTT at 24 hours compared to patients with a therapeutic aPTT at 24 hours.

In 2004 Kearon et al. (25) reported the results of a randomised trial, which demonstrated that fixed weight-adjusted dose subcutaneous unfractionated heparin (initial dose 333 IU/kg followed by 250 IU/kg every 12 h) was as safe and effective as dalteparin or enoxaparin (100 IU/kg every 12 h) for the initial treatment of venous thromboembolism. During three months of follow-up the risk of recurrent venous thromboembolism was 3.8% among those treated with unfractionated heparin compared with 3.4% among those treated with LMWH, and the risk of major bleeding was 1.7% among those treated with unfractionated heparin compared with 3.4% among those treated with LMWH. The aPTT data from this study have not been reported, but the favorable results achieved with unmonitored unfractionated heparin in this study are consistent with the conclusion that the aPTT

is not an important predictor of outcome in patients with venous thromboembolism who receive an adequate dose of unfractionated heparin.

How can these apparently conflicting results be reconciled? The most convincing data supporting a relationship between a subtherapeutic aPTT and risk of venous thrombosis recurrence come from the studies by Hull et al. (12) and by Raschke et al. (16). The Hull study (12) compared two routes of unfractionated heparin administration, but the trial was designed before it was realized that the reduced bioavailability of 30,000 IU/24h of subcutaneous unfractionated heparin would result in lower heparin levels than those achieved by the same dose of intravenous unfractionated heparin. So in effect, two different intensities of unfractionated heparin were being compared. The subcutaneous unfractionated heparin regimen yielded a mean aPTT of 54.8 seconds at 18 hours after the start of treatment compared to the intravenous regimen which yielded a mean aPTT of 71.8 seconds, and the recurrence rate was higher in the patients assigned to receive the subcutaneous regimen. Similarly, the Raschke study (16) compared a suboptimal dose with a more optimal dose of intravenous unfractionated heparin that was adjusted by body weight for the treatment of VTE and found that those receiving suboptimal unfractionated heparin had both a higher frequency of a subtherapeutic aPTT and a higher risk of recurrent venous thrombosis. In both of these studies the risk of recurrent venous thrombosis was higher in patient groups randomised to receive lower starting doses of unfractionated heparin. Not surprisingly those who received the lower intensity dose also had a lower initial aPTT. By contrast, the analyses by Anand et al. (23, 24) were confined to studies in which an adequate initial and maintenance dose of unfractionated heparin was used and found no evidence that the APTT was a clinically important predictor of efficacy, although a weak predictive effect could not be excluded.

The limited value of the aPTT for predicting the efficacy of unfractionated heparin is not surprising. For the test to be a good predictor of outcome, the effect of unfractionated heparin on clinical outcome should be reflected by its effect on the aPTT (8). It has been estimated that less than 50% of the variation in the plasma unfractionated heparin concentration is demonstrable by the aPTT (6, 26, 27), with the remaining variability explained by pre-analytic and analytic variables, and biologic factors that are unrelated to the anticoagulant effect of unfractionated heparin (discussed in more detail below). Unfractionated heparin dose appears to be at least, if not more important than the aPTT as a measure of the plasma unfractionated heparin concentration, and dosage is more important than the aPTT in predicting clinical efficacy.

The relationship between the aPTT and clinical outcome has also been evaluated in patients with arterial disease who are treated with unfractionated heparin. Granger et al. (28) examined the association between aPTT and outcome in 29,656 patients with ST elevation myocardial infarction treated with fibrinolytic therapy who were enrolled in the GUSTO-I trial. Intravenous unfractionated heparin was given as a bolus dose of 5,000 IU and then 1,000 IU/h for at least 48 hours with a target aPTT range of 60 to 85 seconds. An aPTT of 50 to 70 seconds was associated with the lowest 30-day mortality, stroke, and bleeding. There was no convincing increase in risk of cardiovascular events when the aPTT was below 50 seconds but there was an increased risk of reinfarction, stroke, death, and bleeding when the aPTT was greater than 70 seconds. Anand et al. (29) examined the association between aPTT and outcome in 5,058 patients with acute coronary syndromes enrolled in the OASIS-2 trial who were treated with unfractionated heparin for up to 72 hours (29). Intravenous unfractionated heparin was administered as a 5,000 IU bolus followed by an infusion of 15 IU/kg/h with a target aPTT range of 60 to 100 seconds. The risk of bleeding was increased by 7% (95% CI 3–11%) for every 10-second increase in the APTT. There was no significant association between the aPTT and recurrent cardiovascular events or death when the aPTT was analysed as a continuous variable, but patients who had aPTT values of less than 60 seconds were more likely to experience recurrent coronary events (OR 1.54; 95% CI: 1.10–2.15) that those with an aPTT of greater than 60 seconds.

The aPTT data analysed by Granger et al. (28) and Anand et al. (29) were derived from post-hoc analyses from multicentre trials involving multiple laboratories that used many different aPTT reagents. Despite the known poor correlation among aPTT results obtained with different reagents and coagulometers (discussed below), and the poor correlation between aPTT results and unfractionated heparin concentrations, Anand et al. found that the aPTT was a significant predictor of recurrent ischaemic events and bleeding in patients with arterial thrombosis. The association with recurrent ischaemic outcomes was weak and might have been detected because the large sample size provided the high statistical power required to detect a weak signal for an association between aPTT and outcome. The analyses by Granger et al. (28) included an even larger number of patients but did not reveal an aPTT threshold below which there was an increased risk for ischemic events or death. There was, however, an unexplained increase in risk of cardiovascular events in patients with an aPTT greater than 70 seconds (28); an observation which highlights the issue of confounding with post-hoc analyses and does not support an important role for the aPTT when this test is used to monitor unfractionated heparin therapy in arterial thrombosis.

The aPTT should have good precision and be well-standardized among laboratories and for reagents

The aPTT test was first described by Langdell, Wagner, and Brinkhous in 1953 (30, 31) to distinguish hemophilic from normal plasma. The test was initially developed as a two-stage assay but was modified to a one-stage assay in 1958 (32), and was further modified in 1961 (33), which is the test that is used today. It is performed by adding a surface activator and diluted phospholipid to citrated plasma, after which calcium is added and the clotting time is measured.

The aPTT is primarily a measure of the function of the intrinsic and common pathways of coagulation. Numerous factors affect the response of the aPTT to heparin including: pre-analytic variables, such as the methods of sample collection and processing; analytic variables, in particular the combination of the reagent and instrument used to measure the aPTT; and biological variables, which include coagulation factor levels and variables that affect the pharmacokinetics of unfractionated heparin and the dose-response of the aPTT to unfractionated heparin (Table 1) (1, 6). More than 300 different laboratory tests are in clinical use to measure the aPTT (6) and variability in the responsiveness

Table 1: Factors that affect the results of the aPTT to monitor unfractionated heparin therapy. Adapted from references 1, 6, and 7.

Variable	Mechanism
Sample collection and processing	
– Time of blood sampling	Diurnal variation
– Site of blood sampling	Potential for contamination by the infusion
– Citrate concentration	Higher concentrations of citrate affect the test
– Sample transport	Ideally at 2 to 4°C
– Centrifugation	Delayed plasma separation (>1 h) affects the result (PF4 release from platelets)
	Ensure platelet count < 10×10^9/l
Test characteristics	
– Reagent	Variable responsiveness of the reagent to unfractionated heparin
	Variation in reagent according to lot number
– Coagulometer	Differences in methods of end point detection
Biologic variables	
– Unfractionated heparin pharmacokinetics	Altered intravascular volume (obesity, ageing)
	Increased concentrations of heparin binding proteins (infection, inflammation, malignancy)
	Altered unfractionated heparin half-life (hepatic disease, renal disease)
– aPTT dose-response to unfractionated heparin	Increased concentrations of factor VIII, fibrinogen
	Low concentrations of antithrombin (congenital, acute thrombosis, liver disease)
	Reduced concentrations of coagulation proteins (consumptive coagulopathy, liver disease)
– Baseline aPTT	Lupus anticoagulant
	Specific coagulation factor deficiencies (prekallikrein; HMWK; factors XII, XI, IX, VIII)
	Reduced concentrations of coagulation proteins (consumptive coagulopathy, liver disease)

of different reagent-coagulometer combinations has been extensively documented (34–43). Depending on the aPTT reagent and the coagulometer used, aPTT results ranging from 48 to 106 seconds have been obtained from blood samples with an unfractionated heparin concentration of 0.3 IU/ml, as determined using an anti-Xa assay (1, 38, 43). Similarly, aPTT results corresponding to unfractionated heparin levels of 0.3–0.7 anti-Xa IU/ml have been documented to range from 1.6–2.7 to 3.7–6.2 times control (1, 37, 38, 40–48). Based on the above, it is not surprising that a fixed aPTT ratio (e.g. 1.5 to 2.5 times control) or aPTT range (e.g. 50 to 70 seconds) measured with different reagents would not be a good predictor of clinical efficacy. On the other hand, a large study, with a substantial number of events, that uses a single reagent, calibrated against unfractionated heparin levels, might be expected to predict efficacy.

The College of American Pathologists has published consensus guidelines for laboratory monitoring of unfractionated heparin using the aPTT in an attempt to improve precision of the assay (6). Both the American College of Chest Physicians (1) and the College of American Pathologists (6) recommend that individual laboratories develop their own therapeutic range using aPTT values that correspond with accepted therapeutic unfractionated heparin levels. Despite attempts to standardize aPTT monitoring of unfractionated heparin (49, 50), no system of standardization has been widely adopted (1, 51).

Availability and cost of the aPTT

The aPTT assay is rapid, easy to perform, inexpensive, and widely available (6). One of the reasons for its widespread availability is that it is also useful for the diagnosis of coagulation factor deficiencies (27), lupus anticoagulant (52), and possibly thrombophilia (53, 54).

Implications for clinical practice

Despite serious limitations, the aPTT continues to be the most widely used assay to monitor unfractionated heparin therapy in clinical practice. The reliance on the aPTT is likely to continue because of its ready availability and familiarity of clinicians with this test. Accordingly, the focus of clinicians who manage unfractionated heparin therapy should be to ensure that an adequate starting dose of unfractionated heparin is used and that their aPTT method is standardized. An adequate starting dose can be achieved in most patients by using a weight-based nomogram to guide the dosing of intravenous unfractionated heparin (1, 16), or by using a fixed weight-adjusted dose to guide the dosing of subcutaneous unfractionated heparin in patients with VTE. Standardization of the aPTT used to monitor unfractionated heparin can be achieved by following the recommendation that individual laboratories develop their own therapeutic range using aPTT values that correspond to accepted therapeutic unfractionated heparin levels (0.2 to 0.4 IU/ml by protamine titration or 0.3 to 0.7 IU/ml by anti-factor Xa assay). If this type of calibration cannot be performed, the use of an aPTT range of 2.0 to 3.5 times control with modern aPTT reagents is likely to be preferable to an aPTT range of 1.5 to 2.5 which frequently reflects subtherapeutic unfractionated heparin concentrations (22). When very high doses of unfractionated heparin fail to elevate the aPTT into the therapeutic range, dose escalation may be dangerous and can be avoided by monitoring unfractionated heparin therapy and adjusting the dose according to the results of a heparin levels (55).

Implications for research

There is an urgent need to develop methods to improve standardization of the aPTT assay for monitoring unfractionated heparin. Several groups have proposed a method of standardizing aPTT monitoring of unfractionated heparin therapy that involved the use of a reference aPTT method and reference reagent to allow

calculation of a calibration constant for each local aPTT system (49, 50). This approach has the potential to improve the precision of the aPTT for monitoring unfractionated heparin therapy but will not overcome imprecision caused by biologic variables that interfere with the baseline aPTT or the aPTT dose response to unfractionated heparin. Better still, an unfractionated heparin assay could be used to replace the aPTT. Direct measures of unfractionated heparin concentration using either a neutralization or a functional assay are attractive because these assays are not affected by many of the biologic variables that interfere with the aPTT and may be suitable for automation. Currently available unfractionated heparin assays are much more expensive than the aPTT and are not widely available. Outcome studies are also required to investigate the relation between unfractionated heparin dose, the laboratory assay used to measure the anticoagulant effect of unfractionated heparin, and clinical outcome. It is unlikely that such studies will be performed because unfractionated heparin is increasingly being replaced by LMWH for many indications and there are an increasing number of newer anticoagulants being developed to replace unfractionated heparin (56).

Conclusion

Randomized studies indicate that unfractionated heparin is effective in the treatment of thrombosis. A threshold intensity of unfractionated heparin is necessary to obtain efficacy, but the optimal anticoagulant intensity and the appropriate dose required to achieve this intensity is likely to vary among patients. For patients with venous thrombosis, a starting intravenous dose of 35,000 units in the first 24 hours appears to be effective and safe for the vast majority of patients. Since there is a relationship between dose and anticoagulant intensity it was logical to propose that measurement of the anticoagulant effect of unfractionated heparin (reflecting intensity) would provide a useful surrogate for antithrombotic efficacy. Since the anticoagulant effect of unfractionated heparin varies widely among individuals, it is likely, although unproven, that adjusting the dose of unfractionated heparin in patients according to the intensity of its anticoagulant effect improves outcome. Assays to measure unfractionated heparin levels (either through anti-factor Xa or anti-thrombin [IIa] effects) can be standardized, but are not readily available. Although there is a relationship between the unfractionated heparin level and aPTT, the relationship is weak and varies among aPTT reagents, thereby rendering the use of a fixed aPTT ratio or an aPTT range in seconds, problematic. Standardization of aPTT methods used for unfractionated heparin monitoring is recommended, but not widely used. The relationship between unfractionated heparin dose and efficacy in arterial thrombosis is less well established than for venous thrombosis. Accordingly, the validity of the recommended unfractionated heparin levels is less secure. Finally, the relationship between unfractionated heparin dose, anticoagulant intensity and bleeding is less well established. Recent surgery and other invasive procedures are more important risk factors for bleeding than is the starting dose of unfractionated heparin. It is reasonable to assume that a relationship exists between unfractionated heparin dose (and anticoagulant intensity) and bleeding. Such a relationship is likely to be continuous and a threshold dose and threshold intensity measured either as an aPTT or unfractionated heparin level above which the risk of bleeding increases dramatically, has not been established.

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