Monitoring Anticoagulation Therapy in the Critically Ill

Curtis E. Haas, PharmD, BCPS*
Department of Pharmacy
University of Rochester
Medical Center
Rochester, New York, USA

The 2008 National Patient Safety Goals (NPSG) for hospitals, developed by The Joint Commission, recognize the need to minimize patient harm associated with anticoagulation therapy, and The Joint Commission requires all hospitals to have a program in place to meet the expectations of the NPSG by January 2009. Hospitals will be expected to implement a program that provides an individualized care plan for each patient receiving anticoagulant therapy, including appropriate laboratory monitoring, one of the greatest challenges in meeting the NPSG for anticoagulation. Such a program will require consideration as to what represents optimal monitoring to ensure safe and effective anticoagulation therapy for critically ill patients.

The critically ill patient may be at particularly high risk for complications from anticoagulant therapy due to a number of risk factors, including invasive procedures and devices, recent trauma, decreased platelet count and function, coagulopathic states, end-organ failure, and complex concomitant therapies. The underlying severity of illness in the critically ill patient may also alter the pharmacokinetics and pharmacodynamic response to anticoagulant therapy, further increasing the potential risk. In addition, routine laboratory monitoring of anticoagulant therapy may be complicated by changes in the amount or activity of clotting factors, acute phase reactants that may increase non-specific binding of heparin, and antithrombin (AT) deficiency. Data specific to the safety and efficacy of anticoagulant therapy in the critically ill are scarce, and most practices are based on extrapolation from research in predominantly hospitalized, but not critically ill, patients.

Unfractionated Heparin
Unfractionated heparin (UFH) and low-molecular weight heparin (LMWH) are the mainstays of anticoagulant therapy in the intensive care unit (ICU). The response to UFH is unpredictable due to non-specific binding to endothelial cells, monocytes and plasma proteins, contributing to non-linear pharmacokinetic behavior; therefore, routine monitoring of the anticoagulant response is recommended. The activated partial thromboplastin time (aPTT or PTT) is the well-established and recommended monitoring parameter for UFH, but the evidence behind this recommendation is controversial. The PTT is a clot-based, in vitro assay utilizing citrated, platelet-depleted plasma. Although sensitive to the inactivation of thrombin and factor Xa by UFH, the PTT is a non-specific assay. Due to the variable sensitivity of PTT reagents to UFH, the therapeutic range should be a heparin concentration of 0.3 to 0.7 anti-factor Xa U/mL using plasma samples from patients being treated with UFH for thromboembolic disease. This PTT range will be specific for the reagent manufacturer and lot, and coagulometer.

Why was this selected as the target range for UFH? Post hoc analysis of a clinical trial by Basu et al studying the risk of recurrent thromboembolism and an animal study evaluating the prevention of thrombus extension found the effective PTT range corresponded to a heparin concentration of 0.2 to 0.4 U/mL by protamine titration. This was later shown to be equivalent to 0.3 to 0.7 anti-factor Xa U/mL of heparin activity by a single chromogenic assay. There are several reasons why this "shaky foundation" for the therapeutic range is concerning:

- Kitchen et al reported that an anti-factor Xa range of 0.2 to 0.49 U/mL corresponded to a range of 0.2 to 0.4 U/mL by protamine titration assay using the same assay kit as Levine et al. Several methodological issues may explain this difference, but it does raise concern about universal acceptance of 0.3 to 0.7 anti-factor Xa U/mL as being the standard.

- As with other anticoagulant laboratory tests, anti-factor Xa assay results may have poor agreement depending on the methods and reagent kits used. The current recommendations recognize the variability in PTT response, but do not account for variability and standardization of anti-factor Xa heparin activity assays.

- Paired data points comparing PTT and anti-factor Xa activity in ex vivo samples are poorly correlated, with reported r2 values of less than 0.5.2,9 Consistent with this observation, Baker et al reported a 47% concordance rate for clinical decision making between PTT and anti-factor Xa results.

Heparin Resistance
Approximately 25% of adult patients with thromboembolic disease require greater than 35,000 to 40,000 U/day of intravenous UFH to achieve a therapeutic PTT and are considered to be "heparin resistant." This resistance may be either pharmacokinetic or biochemical. Pharmacokinetic resistance may be due to increased non-specific binding of UFH to plasma proteins including platelet factor 4 and histidine-rich glycoproteins, altered effective
in intravascular volume, and increased heparin clearance. Alterations in the PTT dose response to heparin may be due to increased concentrations of fibrinogen and factor VIII, AT deficiency, or a reduction of multiple coagulation factors that may occur with a mild consumptive coagulopathy.1,2,10,11 Based primarily on the work of Levine and coworkers,6 it is widely recommended that caregivers monitor heparin activity by anti-factor Xa in the presence of heparin resistance and adjust the dose to achieve a therapeutic range of 0.3 to 0.7 U/mL.1,2 However, this study – involving a total of 131 patients – was underpowered and did not demonstrate a difference in outcome between the groups with UFH dose adjusted by PTT response versus heparin assay. All the patients monitored by PTT achieved heparin assay results within the proposed therapeutic range.6

Some have advocated for the routine use of heparin assays to monitor UFH therapy because of the numerous limitations of PTT monitoring.9 To date, no study has demonstrated that monitoring heparin plasma activity rather than PTT improves outcome or safety during UFH therapy. The method and instrument used for conducting anti-factor Xa assays also influence the results,7,8,12,13 so using a single therapeutic range appears incorrect. Plasma heparin activity determined by anti-factor Xa assay is essentially a pharmacokinetic endpoint, not a pharmacodynamic measure of UFH response. To serve as a reliable surrogate measure of antithrombotic activity, the variability of the relationship between dose and heparin plasma concentration must be assumed to be greater than the variability between plasma concentration and antithrombotic response. Given the complexity of in vivo coagulation, this is a big assumption. Lastly, since the heparin activity therapeutic range was extrapolated from clinical trials correlating therapeutic outcomes with a target PTT range, to argue that plasma heparin activity is a more reliable surrogate for monitoring response to UFH represents circular logic.

**Low-Molecular Weight Heparins**

For most patients receiving a LMWH for treatment of thromboembolic disease, there is no evidence that routine monitoring can improve effectiveness or decrease the risk of bleeding.1,14,15,16 Anti-factor Xa activity monitoring has been advocated for specific patient groups: the morbidly obese, pregnant women, children, newborns, patients with renal failure, and those requiring prolonged therapy.1,15 The recommended therapeutic target, measured four hours following a subcutaneous (SC) twice-daily dose, is 0.5 to 1.0 U/mL using a chromogenic anti-factor Xa assay; if the patient is receiving a once-daily regimen, the target range is 1.0 to 2.0 U/mL.17 The poor comparability among commercially available anti-factor Xa chromogenic assays,7,8,12,13 an unclear relationship between outcome and anti-factor Xa results, and differences in anti-Xa:anti-IIa ratios for the LMWH products should limit confidence in the routine use of laboratory monitoring for LMWH therapy.1,12,17 The anti-factor Xa assay also must be calibrated to the LMWH product being used.2

Critically ill patients may not exhibit a reliable relationship between standard LMWH doses and anti-thrombotic response due to poor absorption following SC administration, decreased clearance due to renal failure, and altered drug distribution following aggressive volume resuscitation. Several authors have demonstrated altered pharmacokinetics of LMWHs in critically ill patients that may be due to concomitant vasopressor use, hypotension with poor perfusion, or significant peripheral edema.18-21 Therefore, the critically ill should be added to the list of patient groups to be considered for routine pharmacokinetic monitoring of heparin plasma activity by anti-factor Xa assay.

**Alternative Anticoagulants**

Because of increased recognition of heparin-induced thrombocytopenia, the direct thrombin inhibitors (DTIs) – lepirudin and argatroban - increasingly are being used in the critically ill. Laboratory monitoring of response to therapeutic doses of DTIs has been limited primarily to use of the PTT. The recommended therapeutic range for lepirudin is 1.5 to 2.5 times control, whereas the range for argatroban is 1.5 to 3 times control, not to exceed 100 seconds. Due to variable sensitivity of different reagents to DTIs, the use of a single relative range across laboratories is probably inappropriate; however, recommendations to achieve improved standardization of monitoring are not available. The PTT also becomes less responsive with increasing doses of DTIs.17 The institution-specific PTT therapeutic range developed for monitoring heparin therapy should not be used for adjustment of DTI doses. The ecarin clotting time may have advantages for monitoring DTI therapy, but it is not routinely available and has not been adequately evaluated to be considered in place of PTT for routine clinical use.

**Practical Recommendations**

The monitoring of intravenous anticoagulation therapy is imperfect. The most commonly used in vitro, clot-based plasma assay (PTT) has many limitations and does not reliably reflect the status of in vivo hemostasis as described by the currently accepted cell-based model.22 Someday, alternative whole blood assays, such as thromboelastography, may provide a better overall evaluation of the interaction among cells, coagulation factors, and the fibrinolytic system to guide anticoagulation therapy, but researchers are far from having evidence to supplant currently recommended monitoring tests. Despite the many limitations of current monitoring, it is all that is available, and this is unlikely to change in the near future. The PTT should be the primary test used for monitoring UFH therapy, with anti-factor Xa assays reserved for patients requiring high infusion rates to differentiate pharmacokinetic from biochemical heparin resistance. Despite the limitations of anti-factor Xa monitoring for LMWH therapy, the unreliability of SC drug administration in critically ill patients warrants the
routine use of monitoring to assure adequate drug exposure. DTIs should be monitored by aPTT results according to the manufacturers’ recommendations. A multiprofessional approach, including the judicious use of currently recommended tests based on a good understanding of their limitations in the critically ill patient, combined with a thorough knowledge of the available treatment options will contribute to the improved safety of anticoagulation in the ICU. Further research identifying and validating improved monitoring for antithrombotic therapy in the critically ill patient is needed.

References

Disclosures
*Author has no disclosures to report.