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Evaluating the Unfractionated Heparin Sensitivity of new aPTT Reagents

When changing the activated partial thromboplastin time (aPTT) method, a laboratory must determine the responsiveness of the method (reagent/instrument) to unfractionated heparin if the aPTT is to be used to monitor heparin anticoagulation with the aPTT. In order to determine the heparin sensitivity, the laboratory has several options from which to choose, three are listed below. The first is to use a heparin assay to correlate heparin concentration with the new aPTT reagent. The second is to use a cumulative summation method to select a new reagent that has the same heparin responsiveness as the old reagent. The third is to recalibrate the instrument so that the heparin responsiveness of the new method remains the same (or nearly the same) even when the reagents may be different. A summary to the methods follows:

1. Validation of heparin sensitivity of the aPTT using an Assay of Heparin:

This can be done by simultaneously determining the aPTT (seconds) and heparin concentration (U/mL) using samples from patients receiving unfractionated heparin for the treatment of thromboembolism. A dose-response curve can be calculated from the data using regression analysis and the aPTT range corresponding to a heparin concentration of 0.3-0.7 U/mL (by a factor Xa inhibition assay) can be derived.

In contrast to the high degree of correlation between heparin added in vitro and aPTT prolongation, several published comparisons have shown more variability for paired data points comparing the aPTT to heparin concentration in ex vivo specimens, yielding r2 values of <0.50 in many cases. Less than 50% of the variation in aPTTs in heparinized plasmas is explained by differences in the heparin concentrations in those plasmas. In one study, the correlation was better for aPTT/anti-Xa comparisons than for aPTT/protamine titration comparisons suggesting that the functional Factor Xa inhibitory assay may be preferable to the protamine titration assay for establishing the therapeutic interval.

Although the use of the heparin assay may be preferred, the potential burden of such a recommendation should not be overlooked. For example, laboratory validation of the therapeutic range by the performance of simultaneous aPTT and heparin assays may be overwhelming, if not technically infeasible, in small hospitals. An alternative approach is described in section 2 below.

This factor Xa inhibitory comparison method implies that all clinicians will change their behavior, that is, adjust their therapeutic interval for the aPTT, with each change of reagent in the laboratory. Changing the behavior of a diverse group of clinicians can be difficult.

2. Validation of heparin sensitivity of the aPTT using ex vivo heparin specimens: Comparison with an existing, validated aPTT reagent:

The goal of this method is for the laboratory to select a reagent that has the same

(or nearly the same) heparin responsiveness as the one currently in use. By doing so, the clinician behavior need not change. Of importance is to control for, and prevention of, drift with multiple changes over time.