Antifactor Xa activity is not the whole truth, and aPTT is actually sensitive to low levels of low molecular weight heparin

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Anti-factor Xa activity is not the whole truth, and aPTT is actually sensitive to low molecular weight heparins

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Introduction: Low molecular weight heparins (LMWHs) such as enoxaparin (Klexane®) and tinzaparin (Innohep®) are widely used for perioperative thrombosis prophylaxis. Although monitoring is not routine, it is recommended when accurate dosing is especially important, such as in the context of renal impairment, hypercoagulative states or at extremes of weight or age[1].

aPTT (activated partial prothrombin time) is generally not considered sensitive to LMWHs while anti-factor Xa (anti-FXa)activity, which has been shown to correlate well to the concentration of LMWH in the blood [2], is the gold standard for measuring ‘heparin activity’ despite LMWHs’ varying degrees of anti-thrombin (anti-Fila) activity (Table 1).

Method: We present two studies which compare various laboratory tests’ (Figure 1) responses to enoxaparin and tinzaparin added in vitro to blood in concentrations of 0 to 1.5 anti-FXa units/ml. Blood in the first study was sampled from healthy individuals and tested aPTT using four different techniques (free-oscillation rheometry (FOR), Hemochron Jr® and a chromogenic assay using two different reagents), thrombin generation (TG) using two different reagents and anti-FXa activity. The second study used blood sampled at the time of withdrawing epidural catheters from patients who had undergone major surgery and the time of clot initiation was measured with two viscoelastic assays: FOR and thromboelastometry (ROTEM) using reagents activating intrinsic coagulation.

Results and Discussion: Measures of clot initiation with both ROTEM and FOR showed significant dose-responses to increasing concentrations of LMWH, however there was significant inter-individual variation (Figure 2). This also applied aPTT but not measures of clot stability: aPTT correlated well to the concentration of LMWH with correlation coefficients (R) ranging from 0.81 to 0.93 for the different methods tested (Figure 3). The various methods and reagents for measuring aPTT do, however, give differing results. In our study the aPTT’s produced by the ActinFSL reagent were lower than the other methods while the patient-near test Hemochron Jr had slightly lower correlation to the anti-Xa activity. Tinzaparin prolonged the clot time (Figure 4) and aPTT (Figure 5) and inhibited TG more than enoxaparin at equivalent levels of anti-FXa activity. This has been observed in previous studies[3] and would appear to be due to tinzaparin’s stronger anti-FXa activity and Fila being downstream of FXa in the coagulation pathway.

Conclusions: Contrary to popular belief, aPTT is sensitive to LMWH, correlating well to anti-FXa activity. Clinicians must understand that anti-FXa does not measure anti-ila activity and, while it correlates well with the concentration of LMWH in the blood, it does not give the whole truth about the anticoagulative effect. This is reflected in Tinzaparin’s greater prolongation of global coagulation tests such as aPTT and clot initiation, as compared to Enoxaparin. As anti-FXa measures LMWH activity upstream of Fila, it underestimates whole-blood coagulation in less

Figure 1: Two observed limits of thrombin reactivity to various concentrations of LMWHs (Heparin Units/ml) (a) aPTT compared to two in vitro techniques (ROTEM and FOR) (b) Anti-FXa measured with anti-FXa assay (Klexane® and Innohep®). Table 1: Shows the different pharmacodynamic and pharmacokinetic properties of various commonly-used LMWHs (13). Heparin with larger molecular fragments displays a higher anti-FXa activity relative to the antithrombin activity. The property can be expressed as the anti-FXa/anti-heparin ratio.

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