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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2016

Document Version:
Publisher’s PDF, also known as Version of record

Link to publication

Citation for published version (APA):

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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-Xa) 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).

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 for 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 aPTTs produced by the ActinFL 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-Xa activity. This has been observed in previous studies[3] and would appear to be due to tinzaparin’s stronger anti-Fila 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-Xa activity. Clinicians must understand that anti-Fila 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-Fila measures LMWH activity upstream of Fila, it underestimates whole-blood coagulation in less anti-Xa 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.

Anti-Xa and aPTT activity (c)/ How long does it take for the blood to clot (s)?

Table: Ratios displaying the different pharmacokinetic and pharmacodynamic properties of various commonly used LMWH (U/L). Heparins with larger molecular fragments display a higher anti-fx activity relative to the anti-fila activity. The property can be expressed as the anti-Fila/FXa ratio.

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-Xa 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-Xa 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.

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