

Why the big change in the NWH aPTT therapeutic range for heparin?

Change for establishing therapeutic ranges - In keeping with the recommendations put forth by the College of American Pathologists, the laboratory is using the correlations established by the anti-Xa method to determine our aPTT therapeutic range for unfractionated heparin. The information below provides some background information and reasons for making this change.

Why we use heparin - Heparin is a widely used anticoagulant in the treatment and prevention of thrombosis. It is mostly prescribed for acute deep vein thrombosis, pulmonary embolism and postoperatively for vascular surgeries or post myocardial infarction. Heparin binds to antithrombin III to produce the anticoagulant effect by inactivating thrombin and factors X, XII, XI and IX. The rate of inactivation under normal conditions is slow but can be increased several thousand fold by heparin. The aPTT test is used to monitor therapy ensuring that the appropriate antithrombotic effect is obtained.

Need for standardization - The feature story in CAP TODAY Jan. 2004 revealed an unexpected wide variance between institutions' therapeutic anticoagulation ranges for aPTT testing. There is some difference between institutions because of the variation between lots of reagents yet the differences in reagent sensitivity, heparin manufacturing and type of heparin could not account for the wide differences in the therapeutic ranges observed among institutions.

Patient safety issues - Alarmingly, one fifth of the patients in the study didn't make it into the therapeutic range within 24 hours of starting therapy leaving them at increased risk for clotting. One third of the patients entered the supra-therapeutic range on at least two occasions during the first 72 hours of heparin therapy which meant they are more likely to suffer hemorrhagic complications. Considering that heparin has a narrow therapeutic window, failure to bring patients into the therapeutic range – and keep them there- poses a significant patient safety issue.

What we use to do - During the conference on Laboratory Monitoring of Anticoagulant Therapy, CAP stated that it is apparent that laboratories must determine the appropriate therapeutic range for their own aPTT system used to monitor heparin therapy. Annually, Northwest Clinical Laboratory determines the therapeutic range with every lot change in aPTT reagent and IV heparin. Prior to 2008, we used the protamine sulfate titration reference method which involved performing a heparin response curve in vitro by spiking pooled normal plasma with serial heparin concentrations to determine the aPTT values in a range of 0.2 – 0.4 U/mL of heparin. This is no longer the preferred method.

Why the change - The recommended method for establishing the unfractionated therapeutic range is by the anti-Xa method. This method is the most specific and is least affected by the variables inherent to the in vitro technique. Samples are collected from

patients on unfractionated heparin. Patients on warfarin are excluded from testing. The samples are tested with aPTT and anti-Xa assays. Plotting the points in a linear regression determines what range of aPTT values correlate to anti-Xa levels in a range of 0.3 – 0.7 U/mL of heparin. The difference in test principle explains the difference in ranges between protamine sulfate titration and the anti-Xa methods. A heparin therapeutic range for aPTT that falls somewhere between 60 and 100 seconds is fairly average.

Comparison - The NWCL aPTT therapeutic range determined by protamine titration was 40-60 seconds whereas the therapeutic range determined by anti-Xa was 60-100 seconds.

FAQ (frequently asked questions):

- **Why is NWCL using the Xa to determine the therapeutic range for unfractionated heparin?** Correlation of aPTT with the anti-Xa is the preferred method for establishing unfractionated heparin therapeutic ranges because it takes into account patient physiological factors that influence the response to heparin. These include the patient's factor VIII, fibrinogen and anti-thrombin III levels, lupus-like anticoagulants and other drugs the patient might be taking. Spiking normal pooled plasma with various heparin concentrations does not account for patient physiological variables.
- **How does our therapeutic range compare with other area hospitals?** Many of the area hospitals are using the anti-Xa method to determine their therapeutic ranges. Their ranges are consistent with the one we have established.
- **How does Pharmacy and Nursing use the aPTT result?** Pharmacy and nursing use "Order Sets" to adjust the heparin dosage based upon the patient's aPTT result. The Order Set is a set of instructions used to calculate the adjustment of IV heparin based upon the patient's mass and condition.
- **What is unfractionated heparin?** Unfractionated heparin is a heterogeneous mixture of molecules from a biological source with very high molecular weight (15,000-30,000). This heparin is inexpensive and widely used.
- **What is low molecular weight heparin (LMWH) and is it monitored by the same therapeutic range?** Low molecular weight heparin (<5000) cannot bind thrombin and antithrombin III at the same time and therefore are unable to accelerate the inactivation of thrombin by ATIII. LMWH, in theory, does not need constant aPTT monitoring as the antithrombotic effect is much lower. In some cases, monitoring is necessary to determine if the LMWH is effective.
- **Is the aPTT therapeutic range the same for LMWH?** The same therapeutic range for unfractionated heparin is NOT appropriate with LMWH. The usage of LMWH is so low at NWH that we are not able to establish an aPTT therapeutic range. Heparin concentration should be determined by ordering an anti-Xa test.
- **Could we monitor heparin therapy by directly measuring the anti-Xa level instead of using the aPTT test?** Yes. A few hospitals have replaced their aPTT test with an anti-Xa but the anti-Xa testing is very expensive for routine testing.

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