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Clinical Guide - Establishing a Therapeutic Range for Heparin (May 2004)

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Background

Heparin is a widely used drug for the treatment and prevention of venous thromboembolism. The marked inter-individual variability in heparin response results in the need for laboratory monitoring in order to achieve and maintain sufficient heparin concentration to prevent thrombus extension and reduce the risk of bleeding.

A further major source of variability in heparin response is differences in the aPTT reagent/instrument. Each laboratory should establish their own therapeutic range based on the aPTT reagent/instrument used in that lab. For a lab to establish their own therapeutic range for heparin there are two options:

1) for an on-site follow the protocol below;
2) send samples to a reference lab or obtain samples from a reference laboratory.

The current literature suggests that the therapeutic range for heparin therapy should be an APTT between 2.0 and 3.50 times the mean of the normal reference interval. It also has become evident that APTT reagents differ widely in their response to heparin. Given these problems, how does one establish a therapeutic heparin range for their institution? The most common approach is to spike varying concentrations of heparin into normal pooled plasma, and measure the APTT of the plasma samples with these known concentrations of heparin. However, this does not represent an ex vivo response to heparin, and studies have shown that the in vitro dose response curve is almost always higher.

Recommended Protocol

1. Blood is collected from patients (ideally 50) being treated with continuous intravenous heparin. These samples are taken at least 4-6 hours after a heparin bolus but less than 24 hours after the first dose of warfarin.
2. Blood samples are centrifuged at a minimum of 1700G for 15 minutes, the plasma removed to a clean tube, recentrifuged for 5 minutes at 1700G or more. The plasma is frozen at -35°C or lower until testing is performed.
3. The plasma is thawed to 37°C for 5 minutes and the APTT and heparin levels measured.
4. The relationship between APTT and heparin level is plotted using linear regression analysis. The heparin level is plotted on the X axis and the APTT values on the Y axis. The line of best fit is calculated from the regression equation. The therapeutic range for UFH levels is 0.2-0.4 U/ML using protamine sulfate neutralization assay method or 0.35-0.70 U/ML using anti-Xa assays.

An alternate procedure and one that is less onerous is to freeze platelet poor plasma from heparinized patients with known anti Xa heparin levels at -70 C. Before retiring one lot number of APTT reagent, run side by side, aPTT measurements with the current lot number and the new lot number. If the values are within the tolerance of the assay no further work is required. If the aPTTs are different, perform the regression analysis using the anti Xa values previously established or repeat the full procedure described above.

References

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