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Heparin Monitoring

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Introduction: Heparin is widely used for the prevention and treatment of thromboembolic diseases. The anticoagulant response to heparin varies widely among patients, possibly because of variations in the plasma concentrations of heparin-binding proteins. There is evidence that the clinical efficacy of heparin is optimized if the anticoagulant effect is maintained above a defined minimal level and that the risk of bleeding is increased as the dose of heparin increases. For these reasons, the therapeutic use of unfractionated (UF) heparin requires laboratory control, and activated partial thromboplastin times (APTT) and thrombin clotting times (TCT) are most commonly employed. There are clinical situations that make it difficult to monitor heparin by conventional methods and in recent years, low molecular weight (LMW) heparin preparations have increased in clinical use. LMW heparin preparations have lost the ability to prolong the clotting time tests therefore, therapeutic monitoring by the APTT and TCT can no longer be used. Monitoring of the new heparins and difficult clinical situations can be achieved in an anti-Xa system.

Background: Heparin, a naturally occurring polymeric mucopolysaccharide with anticoagulant and antithrombotic properties, is effective in the prevention and treatment of a variety of venous and arterial thromboembolic disorders. It is used as prophylaxis for postoperative thrombosis, in conjunction with the initiation of oral anticoagulant therapy, in the treatment of unstable angina and acute myocardial infarction and to prevent clotting during cardiac bypass.

Commercial preparations of heparin are heterogeneous, their components having molecular weights (mw) ranging from 3,000 to 30,000 (mean, 15,000). Only about one third of the heparin binds to antithrombin III and this fraction is responsible for most of its anticoagulant effect. The remaining two thirds has minimal anticoagulant activity at therapeutic concentrations.

The heparin-antithrombin III complex inactivates a number of coagulation enzymes, including thrombin and activated factors X, XII, XI and IX. Thrombin and activated factor X (factor Xa) are the most sensitive to inactivation. The rate of inactivation , under normal conditions, is slow but can be increased several thousand-fold by heparin. This mechanism accounts for the anticoagulant effect of unfractionated heparin. Low molecular weight heparin preparations (<5400 mw) are unable to bind thrombin and antithrombin III (ATIII) simultaneously and therefore are unable to accelerate the inactivation of thrombin by ATIII, but retain the ability to catalyze the inhibition of factor Xa by ATIII.

Monitoring By APTT: Laboratory monitoring of heparin therapy is desirable to ensure that an appropriate antithrombotic effect is obtained, while guarding against bleeding complications of an overdosage. Currently, the APTT is the most common test used to monitor heparin therapy. Monitoring by APTT evaluates heparin's overall activity throughout the entire coagulation system ie., inactivation of thrombin, Xa, XIIa, XIa and IXa. Heparin treatment is usually monitored to maintain the ratio of the patient's APTT to the mean control APTT within a defined range of approximately 1.5 to 2.5, referred to as the therapeutic range. Laboratory and clinical studies have established a therapeutic range that is equivalent to a heparin level of 0.2 to 0.4 U per milliliter (mL) by protamine titration, or 0.35 to 0.7 U per mL according to the level of anti-Xa activity. It should be noted that the responsiveness of the reagents used in APTT tests can vary widely. The therapeutic range for any given APTT reagent should therefore be established in the clinical laboratory to correspond to a heparin level of 0.2 to 0.4 U/mL by protamine titration.

One of the most common problems encountered is lack of an adequate response to an "adequate" dose. There are two major causes for this; an inadequate dose of heparin or an inadequate response of the APTT to adequate level of heparin.

Monitoring By Anti-Xa Assay: An alternative approach is to assay for heparin exploiting its catalysis by antithrombin III inhibition of coagulation enzymes, particularly factor Xa. The factor Xa inhibition test (anti-Xa assay) is the most useful test for assaying the widest variety of therapeutic heparin preparations. In this method, both factor Xa and antithrombin III are present in excess and the residual factor Xa activity is inversely proportional to the heparin concentration. The assumption is made that the patient has a normal concentration of antithrombin III. For a patient with ATIII deficiency a heparin concentration is measured, but this does not necessarily correspond to the anticoagulant capacity in vivo. It is recommended to also measure the antithrombin III level for all patients under heparin therapy when using this type of assay to ensure normal ATIII activity. The therapeutic range of the anti-Xa assay in the treatment of thromboembolic disease established by laboratory and clinical studies for unfractionated heparin is 0.35 to 0.7 anti-Xa Units/mL. The therapeutic range for LMW heparins has not been well established at this time.

The aim of therapy is to produce truly stabilized levels of circulating heparin capable of maintaining an effective hypocoagulability. There are several clinical situations in addition to the use of LMW heparins, where the specific measurement of heparin levels using the anti-factor Xa method may be necessary. Patients receiving heparin but demonstrating an inadequate APTT response can be evaluated for heparin by the anti-Xa assay. Monitoring of heparin is difficult by conventional methods when the baseline APTT is prolonged as seen in patients with lupus anticoagulants and deficiencies of factor XII (Hagemen factor), prekallikrein (Fletcher factor) and high molecular weight kininogen (Fitzgerald factor). A quantitative anti-Xa assay makes heparin monitoring possible in these clinical situations.

In pregnant women requiring anticoagulation, heparin is the drug of choice because it does not cross the placenta or produce untoward effects in the fetus or newborn when administered to the mother. The effects of LMW heparin on the fetus are not known. The anti-Xa heparin assay can provide accurate monitoring to ensure therapeutic levels are maintained since the long term use of high doses of heparin is associated with osteoporosis.

Summary: It is necessary to re-evaluate the clinical monitoring of the heparin effect, since it has been shown that global clotting assays such as APTT and specific assays such as anti-Xa measure different entities. For standard unfractionated heparins and uncomplicated clinical situations, monitoring by APTT is sufficient. Clinical situations such as a lupus anticoagulant, specific factor deficiencies and pregnancies requiring long term anticoagulation must be monitored by the anti-Xa assay. LMW heparins have high specific anti-Xa activity and low APTT activity. It will not be analytically feasible to monitor heparin therapy with APTT methods. Currently, these drugs can only be monitored by anti-Xa assays.

References:

Hirsh, J. Drug Therapy, N. Engl. J. Med. 1991, 234: 1565-1574.

Hirsh, J., Levine, M.N. Blood. 1992, 79: 1-17.

Copies of Transfusion Medicine Update can be obtained by calling Deborah Small at (412) 622-7254.■

Central Blood Bank's *User's Guide to Products and Services* has been revised and updated. The *Guide* is a comprehensive reference containing important information on blood components, commercial products, special donations and procedures, apheresis, laboratory and clinical services, and the product management and testing policies of CBB. Please contact Barbara Adams (412) 456-1909, if you are interested in receiving a copy.