EDUCATIONAL COMMENTARY - HEPARIN AND THE ACTIVATED PARTIAL THROMBOPLASTIN TIME

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LEARNING OUTCOMES

On completion of this exercise, the participant should be able to:

- discuss the principle of the activated partial thromboplastin time (APTT).
- explain the relationship between the APTT and heparin.
- identify the impact of different types of heparin on the APTT test.

Introduction

The activated partial thromboplastin time (APTT) is a widely available and easy-to-perform test that is useful in

- screening patients with a history of bleeding.
- diagnosing congenital or acquired factor deficiencies.
- determining the presence of lupus anticoagulants.
- evaluating inhibitors to factors VIII, IX, XI, XII, X, V, and II.
- monitoring replacement therapy in patients with known disorders.
- monitoring unfractionated heparin therapy in patients.

The APTT measures the integrity of the intrinsic factors (factors XII, XI, IX, VIII) and the common pathway of coagulation (factors X, V, and II). The test is performed by incubating patient plasma with a phospholipid and an activator. Calcium chloride is added to reverse the effect of the citrated anticoagulant. The APTT represents the time it takes for a clot to form after the addition of calcium and is reported in seconds.

Heparin

Heparin is a rapid-acting anticoagulant that is used in both the prophylaxis and treatment of thromboembolic disorders. Heparin is a glycosaminoglycan extracted from the mast cells of porcine intestinal mucosa or bovine lung. It is a pentasaccharide and serves as a binding site for antithrombin (AT). Heparins are heterogeneous in length and activity; they range in mass from 5,000 to 30,000 kDa. The anticoagulant effect of heparin occurs through interaction with the rate of inhibition of thrombin (IIa) and factor Xa by AT.
Variables in Testing

The type of heparin used and the reagent or instrument used for the APTT test are both analytical testing variables. Many patient factors, such as concurrent medications, also interfere with the action of heparin. Heparin is not well absorbed in the gastrointestinal tract. As a result, there is no dose-response relationship between heparin and the APTT.

In addition, preanalytic variables have a large impact on the APTT and heparin monitoring. These variables include the concentration of citrate in the collection tubes, the volume of blood in the collection tubes, and the time between the administration of heparin and the APTT test. In order to minimize preanalytical variables, collection tubes have been standardized so that the concentration of the tubes uses 3.2% sodium citrate. It has been demonstrated that underfilled tubes decrease the APTT values in heparinized samples. Data also suggest that heparinized samples should be tested within two hours of collection, or the in vivo heparin effect may be underestimated. Centrifugation time is also important; if platelets are present in the sample they may release platelet factor, neutralizing the heparin present.

Heparin Therapy and the APTT

An accepted therapeutic range for the APTT is 1.5 to 2.5 times the mean of the reference range. Blood from a patient with an APTT value within this range is considered to be properly anticoagulated. An association with thrombosis after 24 to 48 hours of receiving heparin has been reported in the literature in patients with an APTT of less than 1.5 times the mean of the reference range. Because laboratories use different types of reagents and patients react differently to the administration of heparin, this formula may not always represent actual heparin levels. It is now recommended that laboratories perform a heparin therapeutic range test to accurately reflect how sensitive their reagent is to heparin.

Heparin Therapeutic Range

A heparin therapeutic range is determined by collecting data from patients who are receiving unfractionated heparin and testing heparin levels using an anti-Xa assay and the APTT test. The anti-Xa assay is not susceptible to many of the preanalytic variables affecting the APTT. A standard curve is constructed using data from unfractionated heparin. The patient’s plasma and a fixed amount of Xa are added. This results in the formation of an inactive AT-Xa complex. The residual Xa will be inversely proportional to the concentration of heparin. Samples within the range of 0.3-0.7 IU/mL are considered therapeutic. Additionally, an APTT test is performed on these samples. The relationship between the heparin levels (quantified in U/mL) and the APTT (quantified in seconds) will result in a therapeutic range expressed in seconds for the instrument and reagent combination in a particular laboratory. This will help validate that the range in seconds corresponds to the circulating heparin levels in the patient.
Low-Molecular-Weight Heparins

Low-molecular-weight heparins (LMWHs) are produced from unfractionated heparin to yield smaller polysaccharides with average molecular masses of 4,000 to 5,000 kDa. These shorter molecules lose the ability to accelerate AT inhibition of thrombin but retain the ability to catalyze factor Xa inhibition. Therefore, although patients on LMWH may have a prolonged APTT, the APTT may not be used to monitor these patients. Decreased in vivo protein binding improves LMWH bioavailability and leads to predictable anticoagulant response. LMWH dosage is weight based; renal excretion and adequate levels can be achieved by subcutaneous administration once or twice daily. It doesn’t require monitoring except in pediatric patients and in patients with renal insufficiency, lupus anticoagulants, cancer, or extremely high or low body weight.

Conclusions

The APTT is an important test for evaluating patients with coagulopathies and in the monitoring of heparin levels. It is a test that has limitations but still provides a tremendous amount of information to clinicians. Heparin anti-Xa assays are an important tool in establishing a heparin therapeutic range. This enables laboratories to optimize their APTT results and to use them to monitor patients on unfractionated heparin. Additionally, the anti-Xa is the only test that can be used when needed to monitor patients on low molecular weight heparin.

Suggested Reading


